Ascertainment Bias Causes False Signal

of Anticipation in Genetic Prion Disease

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Table S1. Correcting for ascertainment bias by including year of birth in parent-offspring regression reduces, but does not eliminate, true signals of heritability.

In order to determine whether our proposed method of including year of birth in parent-offspring regression models to eliminate false signals of heritability would result in false negatives when heritability is truly present, simulations 1-10 from Table 1 were re-run with the same ascertainment conditions but with a different formula for child age of onset. Here, child age of onset was computed as the unweighted mean of (1) a random variable drawn from the original age of onset distribution described in Methods, and (2) parent age of onset. This simulates a scenario in which age of onset is 100% additively heritable – the affected parent contributes half of the child's genome and half of the child's age of onset; the random portion of the child's age of onset represents the contribution from the unaffected parent's genome. Under these conditions, parent-offspring regression without year of birth correctly detects ~100% heritability under all conditions tested. Including year of birth in the model reduces this estimate, particularly in the simulations where ascertainment bias is most extreme (e.g. Simulations 1-2, 4-5), but the signal of heritability is almost always still significant. We conclude that adding year of birth to these regression models is an imperfect but still useful tool. In cases such as Simulation 1, where ascertainment bias has created a large amount of covariance between year of birth and age of onset, we suspect it may simply not be possible to determine how much of the correlation between parent and child age of onset is artifactual versus biological.

Simulation	Direct ascertainment window	Indirect ascertainment	Mean heritability estimate without year of birth	Significant	Mean heritability estimate with year of birth	Significant
1	1989-2013	None	> 100%	100%	41%	88%
2	1950-2013	None	100%	100%	86%	100%
3	1880-2013	None	98%	100%	96%	100%
4	1989-2013	Declining 5%/year	> 100%	100%	60%	100%
5	1950-2013	Declining 5%/year	99%	100%	90%	100%
6	1880-2013	Declining 5%/year	98%	100%	96%	100%
7	1989-2013	Declining 1%/year	98%	100%	65%	100%
8	1950-2013	Declining 1%/year	98%	100%	91%	100%
9	1880-2013	Declining 1%/year	98%	100%	96%	100%
10	1989-2013	Exhaustive	97%	100%	64%	97%