## Supplementary Note

### 1. The influence of sex on the transmission of inherited rare variants in families

Linear regression analysis of trios controlling for cohort, sex and case status shows a negative correlation of DNMs and inhLoF (**Extended Data Fig. 3a**, $P = 0.03$) and no significant gene by sex interaction. This result is consistent with a liability threshold model, with effects that are similar in males and females. These results are also consistent with familial and sporadic ASD having distinct etiologies (i.e. cases that carry damaging DNMs have less inhLoF risk and vise versa).

Based on the model of a female protective effect, we have proposed previously that the differential susceptibility of males and females could result in a bias in the transmission of genetic risk in ASD families[8]. Specifically, we hypothesized that inherited risk might show a biased transmission from the “protected” parent (mothers) to “susceptible” offspring (male cases). However, in this study we did not observe evidence that inhLoF variants were maternally biased, and we did not observe evidence of the predicted mother to son bias in the transmission of inhLoF variants (**Extended Data Fig. 1b**). We did observe a subtle trend of increased mother-to-daughter transmission, suggesting that there could being a maternal bias of inLoF variants when cases are female (and thus may have a greater transmitted genetic load). However, the difference was not statistically significant. Our results suggest that both fathers and mothers contribute substantially to inherited risk.

### 2. Evaluation of PSs calculated using PRSice and SBayesR

During peer review, we evaluated two polygenic scoring methods and, for the final analysis of the dataset, selected the polygenic scoring model with the best prediction accuracy. An initial analysis of our dataset was performed with polygenic scores calculated with PRSice[24], a method that is commonly used in psychiatric genetic studies[56]. As suggested by reviewers, results were confirmed and strengthened using a newer method SBayesR[20]. Here we confirmed in our dataset that SBayesR improves the prediction accuracy of all polygenic scores (**Extended Data Fig. 1**). Overall results were consistent between both methods with one exception. Using PRSice, a sex

difference was observed in the liability threshold effect[24], evident by the negative correlation of de novo/rare variants and polygenic scores, but with polygenic scores calculated using SBayesR, this sex difference was not statistically significant (**Extended Data Fig. 2**). We attribute this difference to an improved power for quantifying polygenic risk in females with SBayesR.