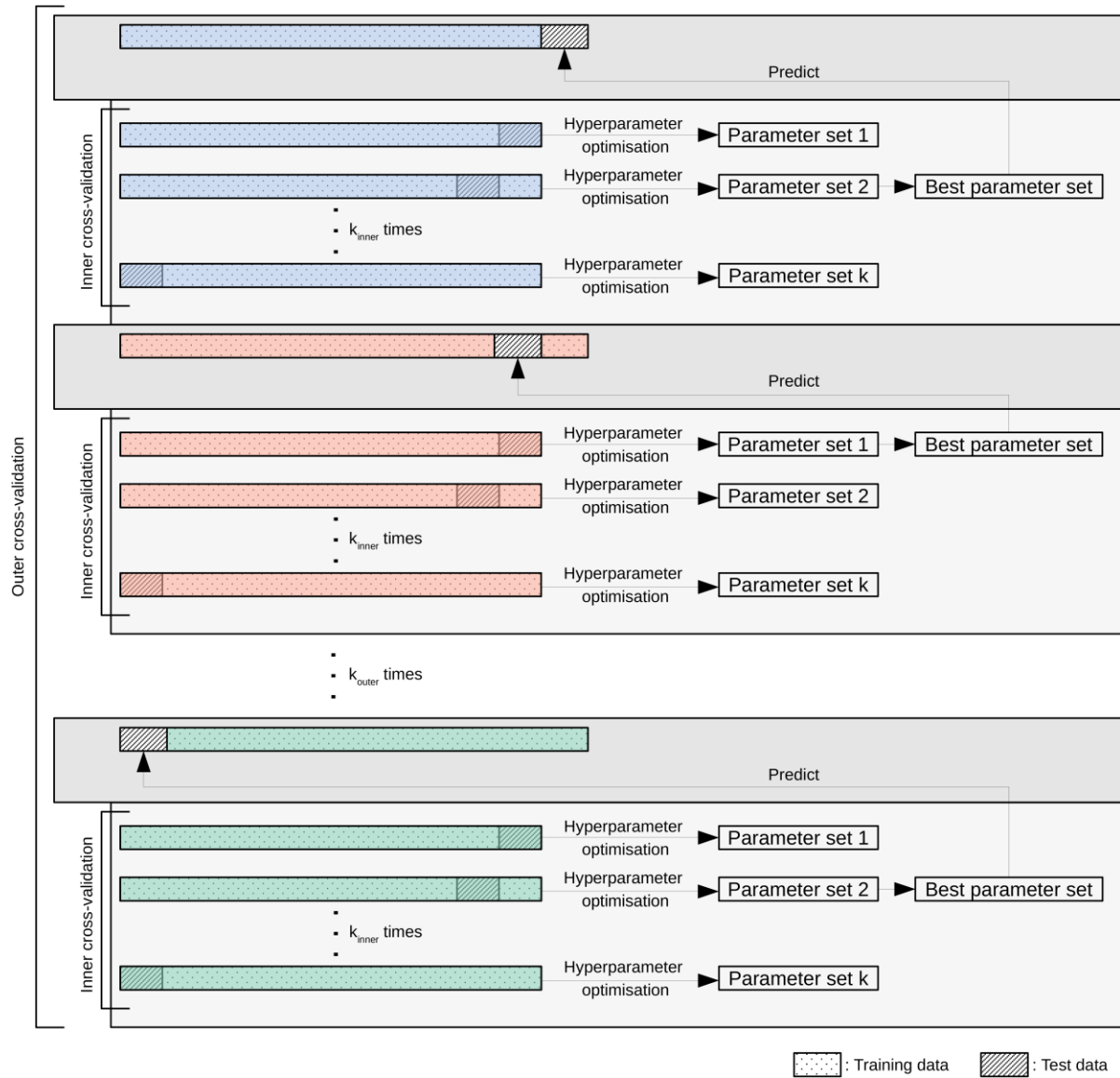


## Supplementary Figure S1: Visualization of the nested cross-validation

Supplement to

*Prediction of function in ABCA4-related retinopathy using ensemble machine learning*



To avoid an optimization bias, the evaluation of the model performance was separated from the hyperparameter tuning by using nested cross-validation. For this, two parameters  $k_{outer}$  and  $k_{inner}$  were chosen. For the outer loop,  $(100/k_{outer}) * (k_{outer}-1)$  % of data was chosen to be the outer training set and the remaining  $(100/k_{outer})$  % were used as the outer test data set. Then, the previously chosen outer training data was iterated over in  $k_{inner}$  steps as described for  $k_{outer}$  creating an inner test and training data set. The models were then trained on the inner training set predicting the inner test set. For each  $k_{outer}$  fold, the hyperparameter set that achieved the best performance on the inner test set was used to predict the outer test set. This was repeated for all  $k_{outer}$  folds. The order of data was randomized before conducting the nested cross-validation to exclude a sorting bias in the data.