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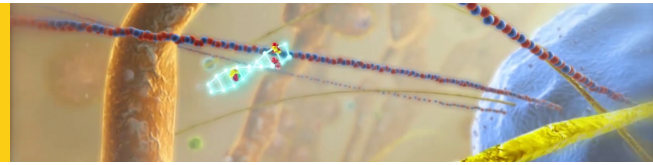
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To treat or not to treat: Predicting Asthma Patient' Responsiveness to Omalizumab Using Machine Learning

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INTRODUCTION

Resistance to inhaled corticosteroids and long-acting β_2 agonist bronchodilators is a major cause of concern for moderate-to-severe-asthma patients. The current treatment option for those patients is the use of biologicals such as the anti-IgE drug omalizumab, as add-on therapy.¹ Despite omalizumab's widely use, patients do not always benefit from this therapy. Therefore, there is an urgent need to identify reliable biomarkers as predictors of Omalizumab response.

OBJECTIVE

Two novel computational algorithms, machine-learning based Recursive Ensemble Feature Selection (REFS)^{2,3} and rule-based algorithm Logic Explainable Networks (LEN)⁴ were used on open accessible mRNA expression data from moderate-to-severe asthma patients to identify genes as predictors of omalizumab response. (See, Fig 1.)

RESULTS

With REFS, the number of features predicting responsiveness was reduced from 28,402 genes to 5 genes (See, Fig 2.) with a cross-validated accuracy of 0.99 (See, Fig 3.). The 5 responsiveness predictive genes encode the following proteins: Coiled-coil domain-containing protein 113 (CCDC113), Solute Carrier Family 26 Member 8 (SLC26A8), Protein Phosphatase 1 Regulatory Subunit 3D (PPP1R3D), C-Type lectin Domain Family 4 member C (CLEC4C) and LOC100131780 (not annotated). The LEN algorithm found 4 identical genes with REFS: CCDC113, SLC26A8 PPP1R3D and LOC100131780, which are all upregulated in non-responders and downregulated in responders (See, Fig 4.) Literature research showed that the 4 identified responsiveness predicting genes are associated with mucosal immunity, cell metabolism, and airway remodelling.

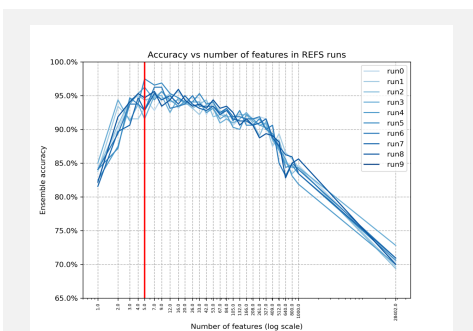


Fig. 2 Peak accuracy with 5 selected genes The REFS algorithm uses classifiers and runs 10x for decision making. The results of REFS for the classification of treatment response in moderate-to-severe asthma patients is shown here. The X axis cuts at 5, suggesting that 5 genes are best for response prediction. The 5-gene signature corresponds with the highest peak in accuracy over all 8 classifiers in the REFS ensemble.

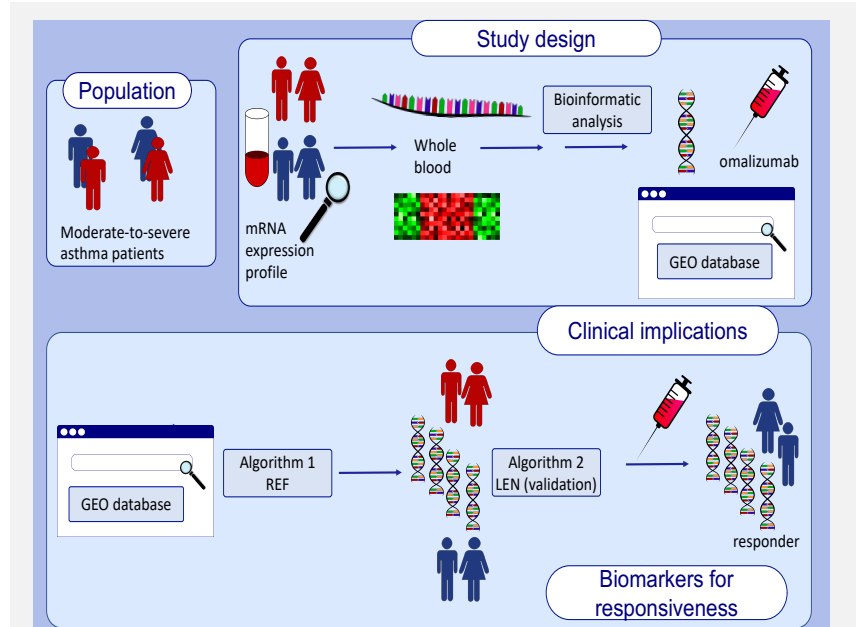


Fig. 1 Methodology. Whole blood transcriptomic analysis of moderate-to-severe asthma patients treated with omalizumab using clinical array data from GEO database. Two novel algorithms identify response-predictive genetic biomarkers for omalizumab. 4 identical response-predictive biomarkers returned from both algorithms may be used in clinic to select patients for omalizumab therapy

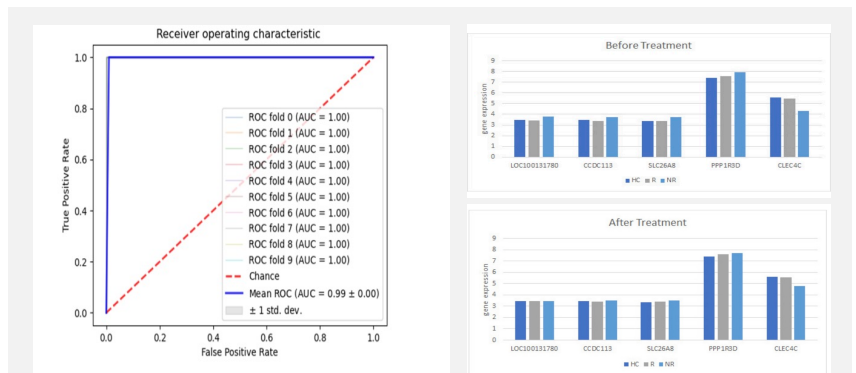


Fig. 3 ROC curve from REFS The curve shows threshold from 0 (all moderate-to-severe asthma patients as responder and both TPR and FPR =1; upper right corner of ROC) to 1 (all moderate-to-severe asthma patients classified as non-responder to therapy and both TPR and FPR=0; lower left corner of ROC). The AUC is the area in the plot which stays under the ROC curve. The classifier producing blue ROC curve shows optimum predictive accuracy as it covers a larger area compared to the straight ROC curve with the random classifier (red dashed line).

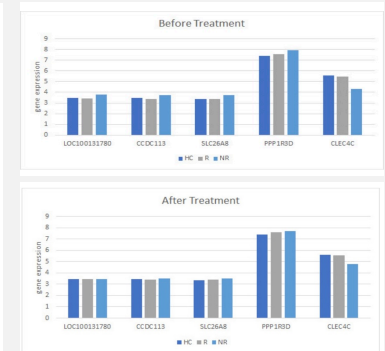


Fig. 4 Comparison gene expression among groups pre- and post Omalizumab treatment. Comparing both approaches an overlap of four genes was found. The relationship between responder status (R/NR/HC) is shown in the bar graph.

Comments and suggestions are welcome:
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CONCLUSION

Both REFS and LEN machine learning methods show 4 identical genes as predictors of omalizumab response in moderate-to-severe asthma patients. The obtained high accuracy indicates that our approach has potential in clinical settings. Future studies in relevant cohort data should validate our computational approach.

REFERENCES

- Masoli, M., Fabian, D., Holt, S., Beasley, R., & Global Initiative for Asthma (GINA) Program (2004). The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*, 59(5), 469-478. <https://doi.org/10.1111/j.1398-9995.2004.00526.x>
- Lopez-Rincon, A., Mendoza-Maldonado, L., Martinez-Archundia, M., Schönhuth, A., Kraneveld, A. D., Garssen, J., & Tonda, A. (2020). Machine Learning-Based Ensemble Recursive Feature Selection of Circulating miRNAs for Cancer Tumor Classification. *Cancers*, 12(7), 1785. <https://doi.org/10.3390/cancers12071785>
- Lopez-Rincon, A., Martinez-Archundia, M., Martinez-Ruiz, G. U., Schönhuth, A., & Tonda, A. (2019). Automatic discovery of 100-miRNA signature for cancer classification using ensemble feature selection. *BMC bioinformatics*, 20(1), 480. <https://doi.org/10.1186/s12859-019-3050-8>
- Barbiero, P., Ciravegna, G., Giannini, F., Liu, P., Gori, M., & Melacci, S. (2022, June). Entropy-based logic explanations of neural networks. In *Proceedings of the AAAI Conference on Artificial Intelligence* (Vol. 36, No. 6, pp. 6046-6054).
- Kidwai, S., Barbiero, P., Meijerman, I., Tonda, A., Perez-Pardo, P., Liu, P., van der Maitland-Zee, A. H., Oberski, D. L., Kraneveld, A. D., & Lopez-Rincon, A. (2023). A robust mRNA signature obtained via recursive ensemble feature selection predicts the responsiveness of omalizumab in moderate-to-severe asthma. *Clinical and translational allergy*, 13(11), e12306. <https://doi.org/10.1002/ct2.12306>