



HAL
open science

USING MACHINE LEARNING FOR DRUG DISCOVERY IN IBD

Sarah Kidwai, David Rojas-Velazquez, Dora Kožinec, Lukas Vaišvilas, Paula
Perez-Pardo, Alejandro Lopez-Rincon

► **To cite this version:**

Sarah Kidwai, David Rojas-Velazquez, Dora Kožinec, Lukas Vaišvilas, Paula Perez-Pardo, et al.. USING MACHINE LEARNING FOR DRUG DISCOVERY IN IBD. CMBBE 2023 - 18th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering (CMBBE 2023), May 2023, Paris, France. hal-04097613

HAL Id: hal-04097613

<https://hal.science/hal-04097613v1>

Submitted on 15 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

USING MACHINE LEARNING FOR DRUG DISCOVERY IN IBD

Sarah Kidwai (1), David Rojas-Velazquez (1,2), Dora Kožinec(1), Péter Tózsér(1), Lukas Vaišvilas(1), Paula Perez-Pardo(1), Alejandro Lopez-Rincon (1,2)

1. Utrecht University, Pharmacology, Netherlands; 2. Julius Center UMC Utrecht, Netherlands

1. Introduction

Inflammatory Bowel Disease (IBD) refers to two conditions: ulcerative colitis (UC) and Crohn disease (CD) [1]. IBD has a range of clinical symptoms including abdominal pain, diarrhoea, weight loss, constipation, and fatigue [2]. The main cause of IBD is unknown, but it is the result of a weakened immune system. The possible causes of IBD involve genetic and environmental factors. Unfortunately, with conventional diagnostic methods it is hard to predict therapeutic responsiveness of patients beforehand [3]. Genetic expression may be a valuable prediction tool to determine patient's responsiveness to treatment.

2. Materials and Methods

mRNA data from *Arijs et al* [4] was analysed with Recursive Ensemble Feature Selection (REFS). The data has 120 colonic biopsies of patients and 12 healthy controls. The REFS algorithm uses 8 classifiers from the sci-kit toolbox [5] in a nested 10-fold cross-validation and then we validate our results with 5 new classifiers to avoid overfitting. Finally, as a measure for diagnostic accuracy we used the ROC curve[6].

3. Results

5 resulting features were selected from the original 33252: 7922994 (*FAM5C*), 7905881 (*ADAM15*), 7894470 (N/A), 7995803 (*MTIJP*) and 7927288 (*SHLD2P3*).

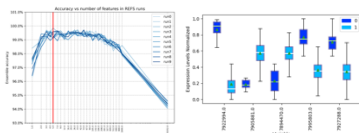


Figure 1: 10 runs of REFS algorithm, with best answer at 5 genes (left). Boxplot of the 5 selected features comparison between healthy controls and IBD (right).

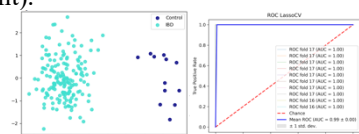


Figure 2: PCA plot of IBD and control groups (left), ROC Curve with an AUC of 0.99 using the 5 selected features(right).

4. Discussion and Conclusions

FAM5C is the most important gene found by REFS to differentiate IBD patients compared to healthy controls. In colonic tissue, gene expression sites are mainly located in the cytoskeleton region of the brush border membrane. Smith et al. suggested that *FAM5C* under expression may cause membrane damage in patients, therefore serving as a susceptibility factor for IBD [7]. *FAM5C* expression is upregulated by inflammatory stimuli such as TNF- α [8]. By inhibiting proinflammatory pathways such as NF- κ B, increased *FAM5C* expression could be reversed. These results correlate with new IBD therapy, Cyclosporine's effects. Cyclosporine decreases the expression of *FAM5C*, and it is also a NF- κ B and JNK inhibitor [9].

5. References

- [1] Sairenji, T., Collins, K. L., & Evans, D. V. (2017). An Update on Inflammatory Bowel Disease. *Primary Care: Clinics in Office Practice*, 44(4), 673–692. <https://doi.org/10.1016/j.pop.2017.07.010>
- [2] Flynn, S., & Eisenstein, S. (2019). Inflammatory Bowel Disease Presentation and Diagnosis. *Surgical Clinics of North America*, 99(6), 1051–1062. <https://doi.org/10.1016/j.suc.2019.08.001>
- [3] Wang, M. H., Fritton, J. J., Raffals, L. E., Leighton, J. A., Pasha, S. F., Picco, M. F., Cushing, K. C., Monroe, K., Nix, B. D., Newberry, R. D., & Faubion, W. A. (2019). Novel Genetic Risk Variants Can Predict Anti-TNF Agent Response in Patients with Inflammatory Bowel Disease. *Journal of Crohn's & colitis*, 13(8), 1036–1043. <https://doi.org/10.1093/ecco-jcc/jjz017>
- [4] Arijs, I., De Hertogh, G., Lemmens, B., Van Lommel, L., de Bruyn, M., Vanhove, W., ... & Vermeire, S. (2018). Effect of vedolizumab (anti- α 4 β 7-integrin) therapy on histological healing and mucosal gene expression in patients with UC. *Gut*, 67(1), 43–52.
- [5] Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., ... & Duchesnay, E. (2011). Scikit-learn: Machine learning in Python. *The Journal of machine Learning research*, 12, 2825–2830.
- [6] Šimundić, A. M. (2009). Measures of diagnostic accuracy: basic definitions. *ejifcc*, 19(4), 203.
- [7] Smith, P. J., Levine, A. P., Dunne, J., Guilhamon, P., Turmaine, M., Sewell, G. W., O'Shea, N. R., Vega, R., Paterson, J. C., Oukrif, D., Beck, S., Bloom, S. L., Novelli, M., Rodriguez-Justo, M., Smith, A. M., & Segal, A. W. (2014). Mucosal transcriptomics implicates under expression of BRINP3 in the pathogenesis of ulcerative colitis. *Inflammatory Bowel Diseases*, 20(10), 1802–1812. <https://doi.org/10.1097/MIB.0000000000000169>
- [8] Sato, J., Kinugasa, M., Satomi-Kobayashi, S., Hatakeyama, K., Knox, A. J., Asada, Y., Wierman, M. E., Hirata, K. I., & Rikitake, Y. (2014). Family with Sequence Similarity 5, Member C (FAM5C) Increases Leukocyte Adhesion Molecules in Vascular Endothelial Cells: Implication in Vascular Inflammation. *PLOS ONE*, 9(9), e107236. <https://doi.org/10.1371/JOURNAL.PONE.0107236>
- [9] Weissman, S., Chris-Olaiya, A., Mehta, T. I., Aziz, M., Alshati, A., Berry, R., Fatima, R., Kolli, S., Hassan, A., & Sciarra, M. A. (2019). A novel player: cyclosporine therapy in the management of inflammatory bowel disease. *Translational Gastroenterology and Hepatology*, 4. <https://doi.org/10.21037/TGH.2019.08.08>