HELLENIC REPUBLIC
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pMedGR

ΑΠΟΡΡΥΘΜΙΣΗ ΤΩΝ ΕΠΙΔΙΟΡΘΩΤΙΚΩΝ ΜΗΧΑΝΙΣΜΩΝ ΤΗΣ ΒΛΑΒΗΣ ΤΟΥ DNA ΣΤΗ ΝΟΣΟ ΑΔΑΜΑΝΤΙΑΔΗ-ΒΕΗΣΕΤ

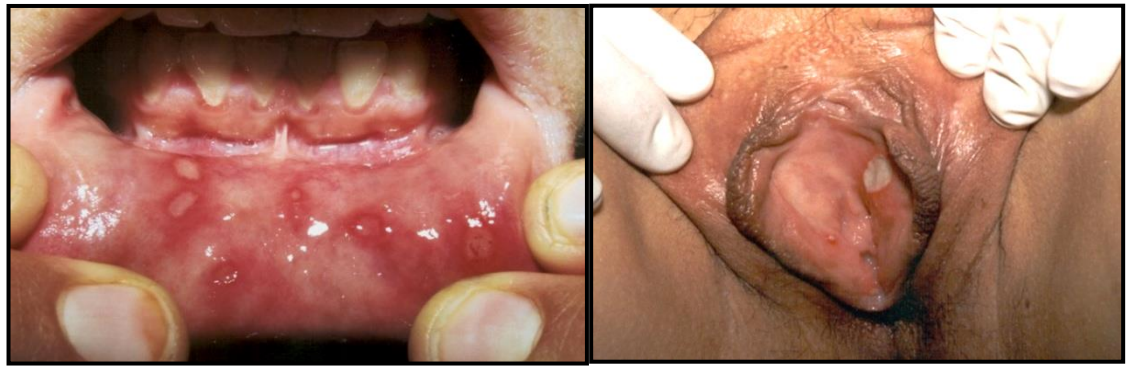
Βλαχόγιαννης Ν.Ι.*, Ντούρος Π.Α.*, Παππά Μ., Βέρρου Κ.-Μ., Αρίδα Α., Σουλιώτης Β., Σφηκάκης Π.Π.

14ο Ετήσιο Πανελλήνιο Συνέδριο ΕΠΕΜΥ – Ρόδος 2022

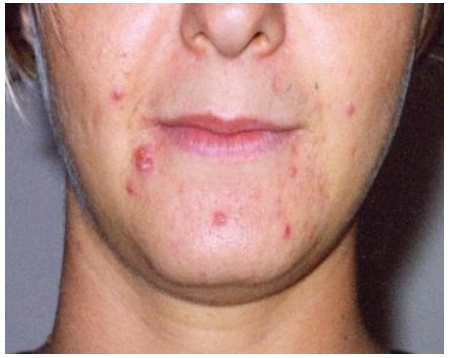
ABD: distinct, chronic, relapsing, multisystem inflammatory disease

- small and large vessels of venous and arterial systems affected
- typical time of diagnosis: 3rd-4th decade...very rare in children
- recurrent oral ulcers (90% first symptom) may appear years BEFORE diagnosis…

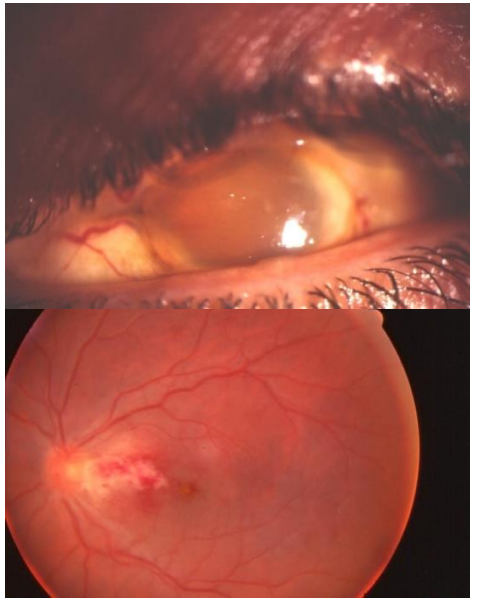
oral and genital ulcers



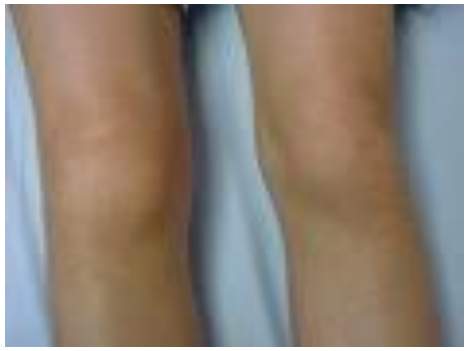
pseudofolliculitis



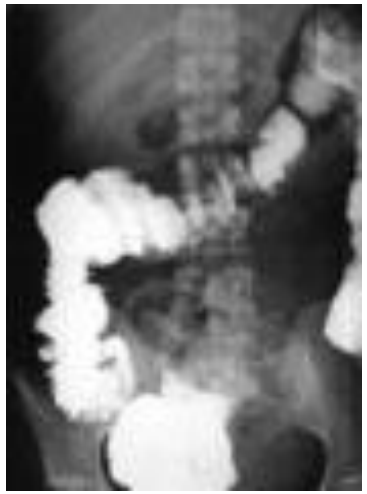
ocular disease



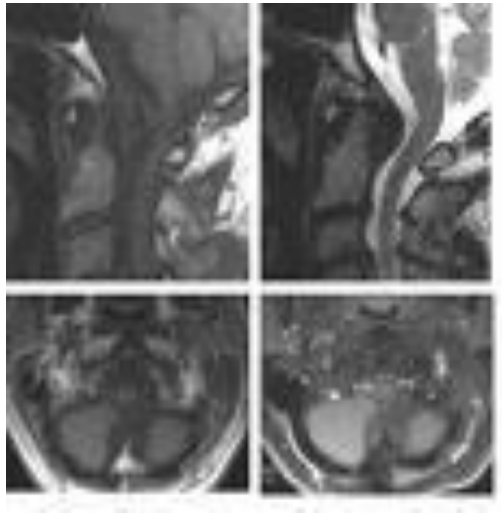
arthritis



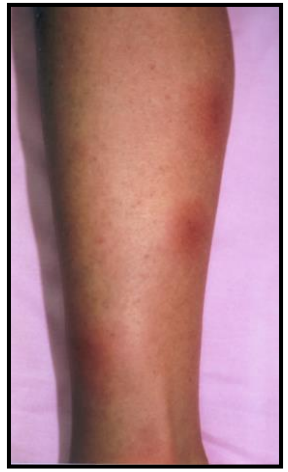
GI



CNS



erythema nodosum



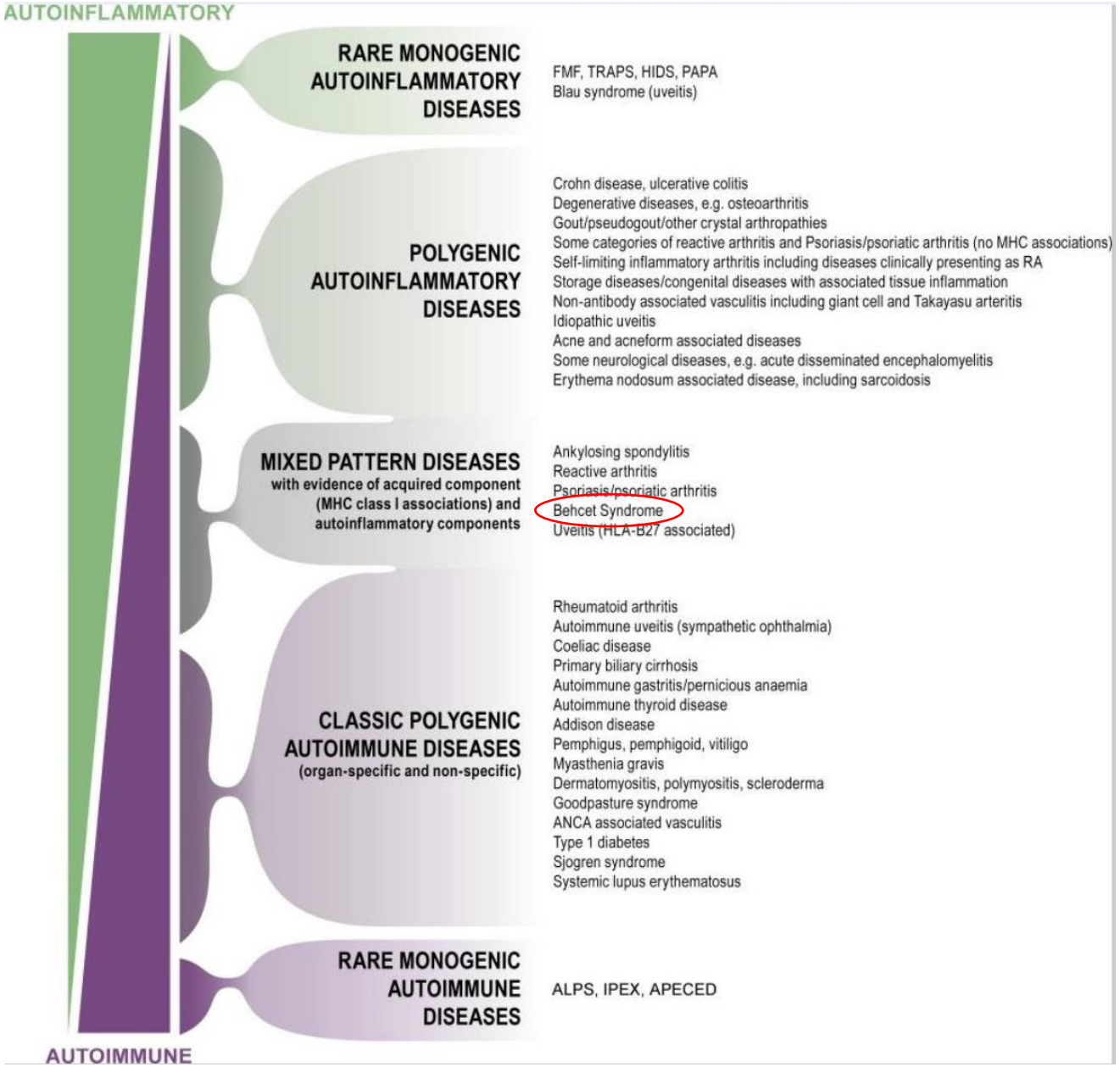
(slide kindly provided by PP Sfikakis)

ABD lies at the intersection of autoimmunity and autoinflammation

OPEN ACCESS Freely available online PLOS MEDICINE
Research in Translation

A Proposed Classification of the Immunological Diseases

Dennis McGonagle*, Michael F. McDermott



NEIL1 is associated with BD at the genetic level

The DNA repair enzyme **NEIL1** has been identified as one of the two genetic risk factors for BD by whole exome study in 3 independent patient cohorts

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 5, May 2016, pp 1272–1280
DOI 10.1002/art.39545

Whole Exome Sequencing Identifies Rare Protein-Coding Variants in Behçet's Disease

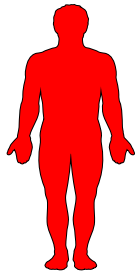
Mikhail Ognenovski,[1] Paul Renauer,[1] Elizabeth Gensterblum,[1] Ina Kötter,[2] Theodoros Xenitidis,[3] Jörg C. Henes,[3] Bruno Casali,[4] Carlo Salvarani,[4] Haner Direskeneli,[5] Kenneth M. Kaufman,[6] and Amr H. Sawalha[1]

Methods. **Whole exome sequencing was performed in a discovery set comprising 14 German BD patients of European descent. For replication and validation, Sanger sequencing and Sequenom genotyping were performed in the discovery set and in 2 additional independent sets of 49 German BD patients and 129 Italian BD patients of European descent. Genetic association analysis was then performed in BD patients and 503 controls of European descent. Functional effects of associated genetic variants were assessed using bioinformatic approaches.**

Results. **Using whole exome sequencing, we identified 77 rare variants (in 74 genes) with predicted protein-damaging effects in BD. These variants were genotyped in 2 additional patient sets and then analyzed to reveal significant associations with BD at 2 genetic variants detected in all 3 patient sets that remained significant after Bonferroni correction. We detected genetic association between BD and *LIMK2* (rs149034313), involved in regulating cytoskeletal reorganization, and between BD and *NEIL1* (rs5745908), involved in base excision DNA repair ($P = 3.22 \times 10^{-4}$ and $P = 5.16 \times 10^{-4}$, respectively). The *LIMK2* association is a missense variant with predicted protein damage that may influence functional interactions with proteins involved in cytoskeletal regulation by Rho GTPase, inflammation mediated by chemokine and cytokine signaling pathways, T cell activation, and angiogenesis (Bonferroni-corrected $P = 5.63 \times 10^{-14}$, $P = 7.29 \times 10^{-6}$, $P = 1.15 \times 10^{-5}$, and $P = 6.40 \times 10^{-3}$, respectively). The genetic association in *NEIL1* is a predicted splice donor variant that may introduce a deleterious intron retention and result in a noncoding transcript variant.**

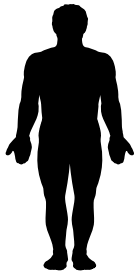
Ognenovski et al., Arthritis Rheumatol., 2016

Study design



26 BD patients

23 men
Age: 40.7±9.9 years
17 with active disease



26 age- and sex-matched
healthy controls

23 men
Age: 38.4±12.1 years

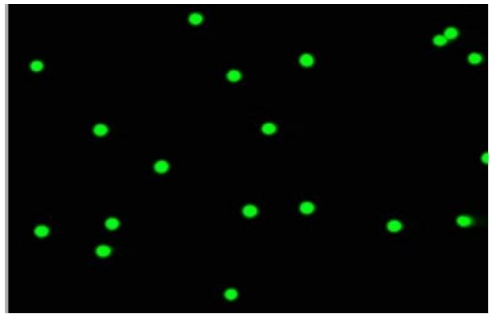
Peripheral blood mononuclear cell (PBMC) isolation

Methods

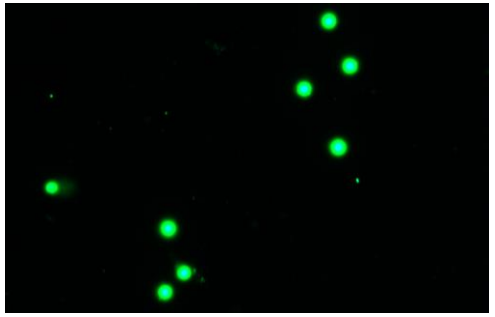
- Endogenous DNA damage measurement (alkaline comet assay)
- DNA repair capacity [nucleotide excision repair (NER)]
- RNA-sequencing: expression levels of key DNA repair enzymes and senescence markers / factors

Endogenous DNA damage is increased in active BD

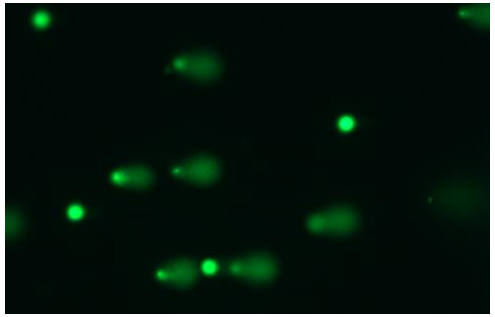
HC

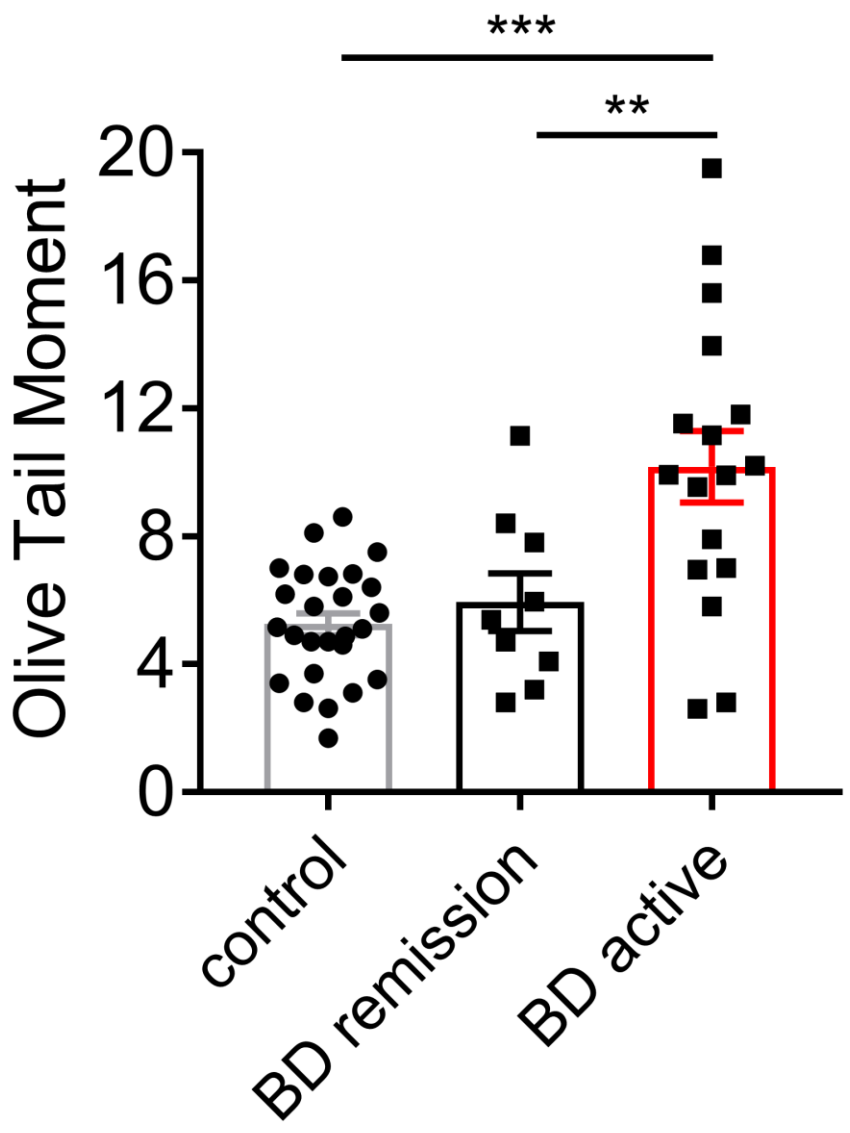


BD in remission

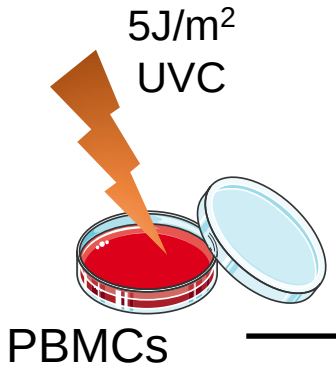


active BD





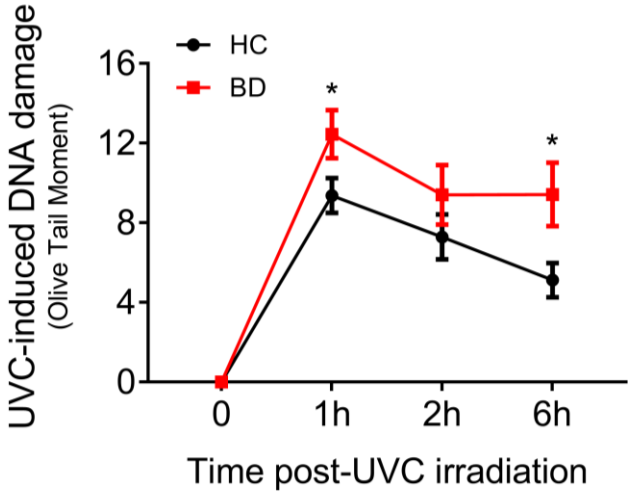
Defective nucleotide excision repair in BD



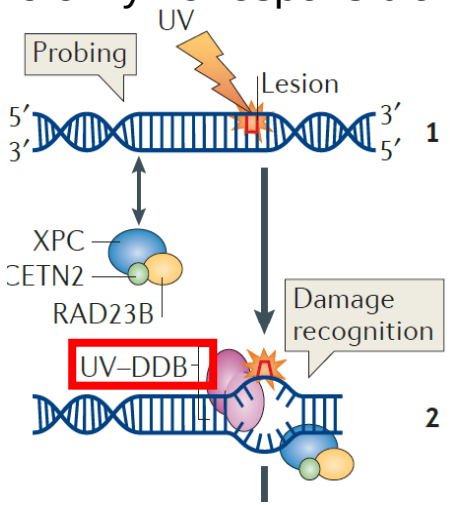
1h
2h
6h

Collect cells for comet assay

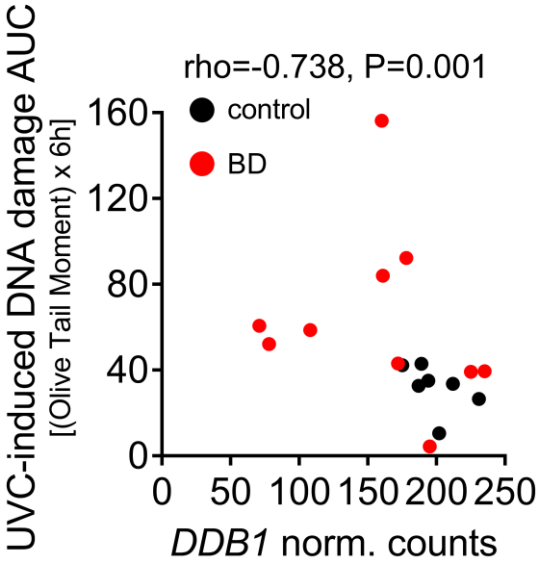
Defective repair of DNA damage induced by UV in BD



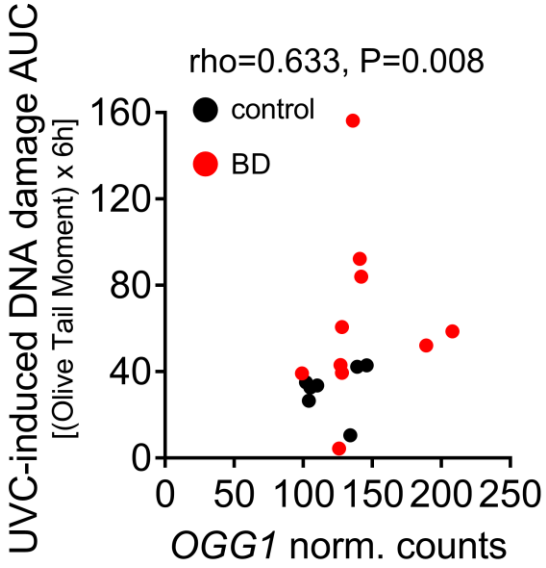
Negative correlation of UVC-induced DNA damage with **DDB1**, the enzyme responsible for recognition of UV-induced lesions



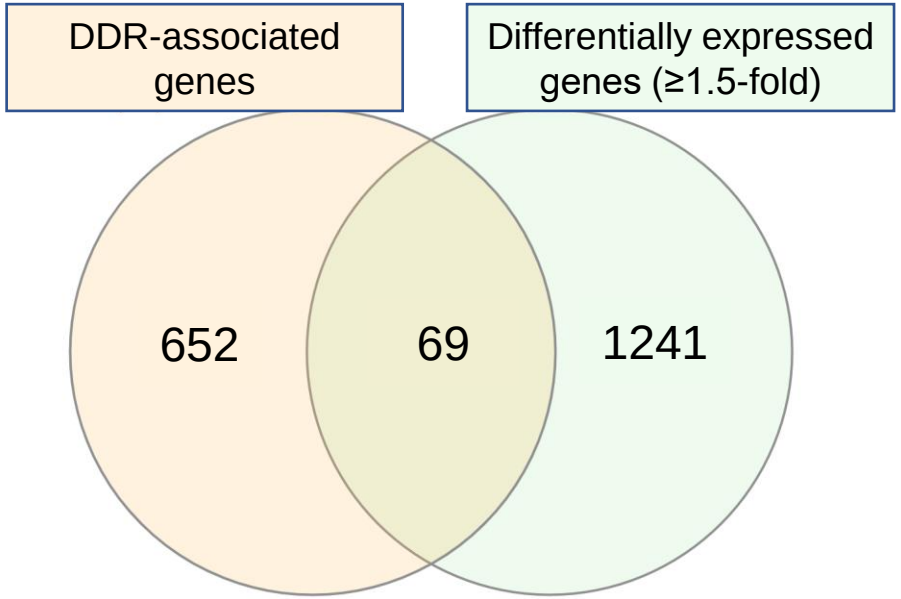
Marteijn JA et al., Nat Rev Mol Cell Biol., 2014



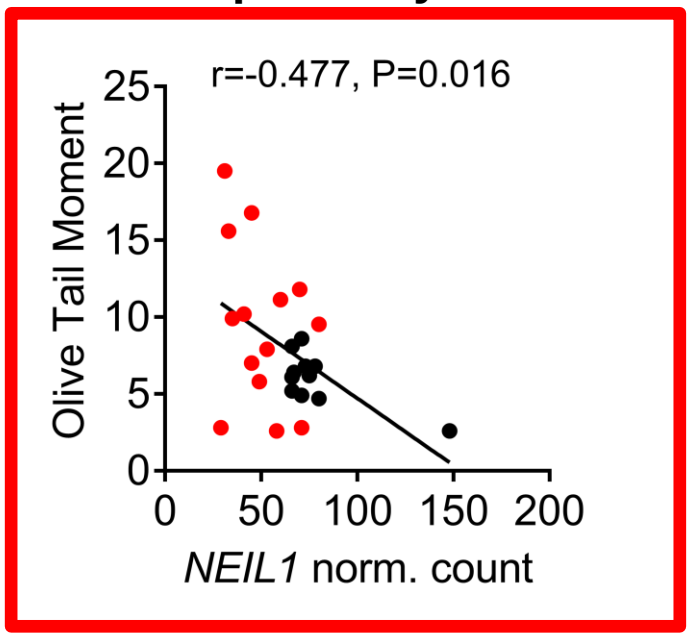
Positive correlation of UVC-induced DNA damage with **OGG1**, which promotes subsequent proinflammatory gene expression



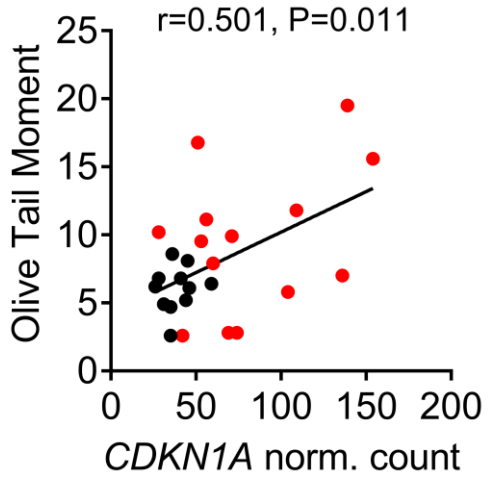
Association of increased endogenous DNA damage with deregulated gene expression in patients with BD

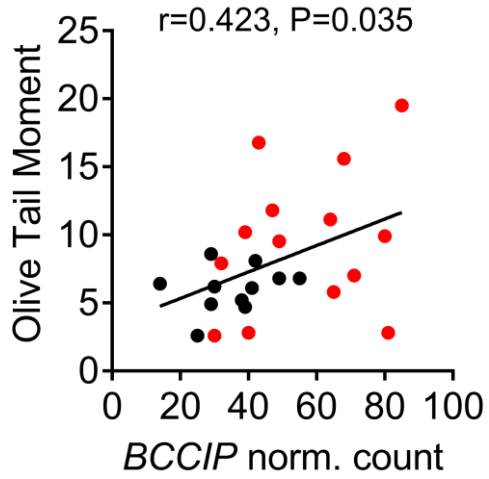


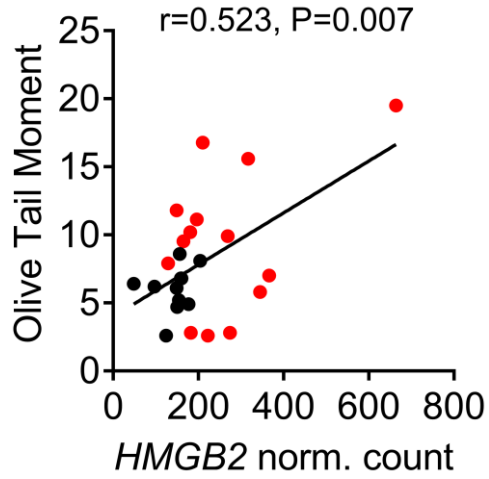
1. DNA repair enzyme NEIL1



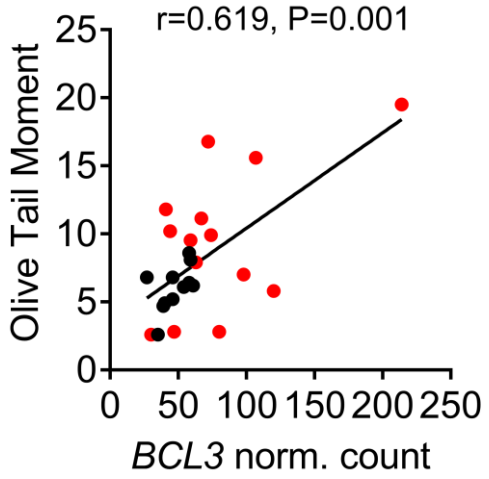
2. Senescence-associated factors

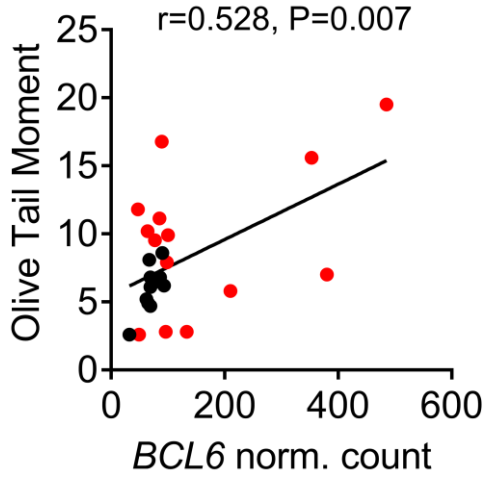






3. Anti-apoptotic factors





…to conclude…

- Increased DNA damage accumulation is present only in patients with active BD and not in those in remission.

- Reduced expression of *NEIL1*, previously associated at the genetic level with BD, may underlie increased DNA damage accumulation in BD.

- Deregulated DNA damage response may participate in shaping the proinflammatory, senescence-associated transcriptomic profile observed in BD patients.

Thank you!

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