PIEZO1 variants that reduce open channel probability are associated with familial osteoarthritis and have distinct roles in injury and aging

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Background

Cells of the synovial joint sense (mechanosensing) and respond (mechanotransduction) to daily physical forces to maintain homeostasis of the joint. Disruption of mechanosensing or mechanotransduction can lead to molecular and cellular changes in the joint that are associated with the development of osteoarthritis (OA).

PIEZO1 is a major mechanosensitive cation channel in the joint directly regulated by mechanical stimulus. Genetic studies in mice have indicated that loss of PIEZO1 in cartilage is protective against injury induced OA. A recent *in vitro* study has demonstrated that activation of PIEZO1 with a chemical agonist promotes expression of pro-chondrogenic genes and increased deposition of sulfated glycosaminoglycans. These data suggest that PIEZO1 may have context dependent roles in maintaining homeostasis of the joint.

Despite the significant genetic contribution to OA, there is only one reported genetic association of *PIEZO1* variants with the OA phenotype. The genetic analysis of families with dominant forms of OA allows us to identify highly penetrant coding alleles that have a determinate effect on promoting OA, independent of prior biases on how protein activity may affect the OA phenotype or the tissues specific requirement of the mutant alleles.

We hypothesize that PIEZO1 may have context dependent or tissue specific roles in injury vs aging.

Proposed role of PIEZO1 in cartilage and OA development

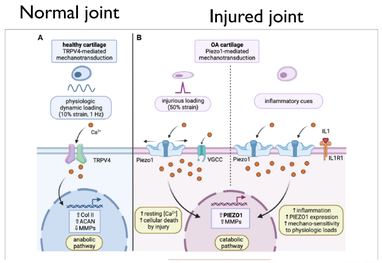


Figure from Gao et al, 2022

***Piezo1* KO mouse**	***PTOA phenotype compared with WT***	
Gdf5-Cre -	No effect	Young and Kobayashi, 2023
Col2-Cre -	Protected	Brylka et al, 2024
Agg-Cre -	Protected	Ely et al, 2025
Procr-Cre -	Accelerated	Zhu et al, 2025

PIEZO1 is thought to have a role primarily in the response to injury where it regulates inflammatory signaling to promote OA.

Identification of families with PIEZO1 mutations

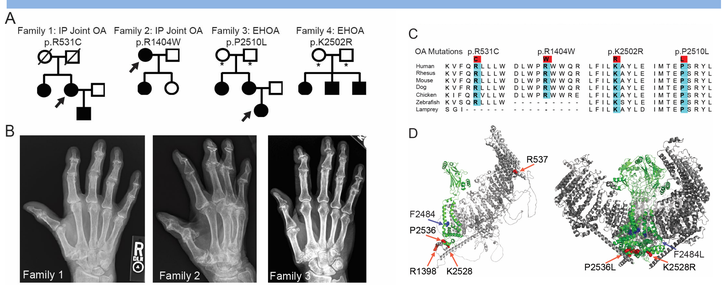


Table 1. PIEZO1 Variants Identified in Independent Osteoarthritis Families and through GWAS

OA Phenotype (Family)	Human Variants (Mouse amino acid)	Minor Allele Frequency	Functional Effect
Finger Interphalangeal Joint OA (FIJ876)	p.R531C (p.R537)	0.0005	Loss-of-function
Erosive Hand OA (ERO13)	p.K2502R (p.K2528)	0.006	Loss-of-function
Erosive Hand OA (ERO15)	p.P2510L (p.P2536)	0.006	Loss-of-function
Finger Interphalangeal Joint OA (FIJ126)	p.R1404W (p.R1398)	0.0007	Loss-of-function
Reduced Hip OA Progression (GWAS)	p.F2458L (p.F2484)	0.001	Gain-of-function

Figure 1. (A and B) We identified 4 *PIEZO1* mutations that segregate with familial forms of hand OA. (**C and D)** The *PIEZO1* mutations are in conserved residues and cluster near of the pore. **Table 1.** A rare coding variant was identified in a GWAS that was associated with individuals who have OA, but do not progress to need a joint replacement (Henkel, et al, 2023).

The familial PIEZO1 alleles are hypomorphic while the GWAS allele is hypermorphic

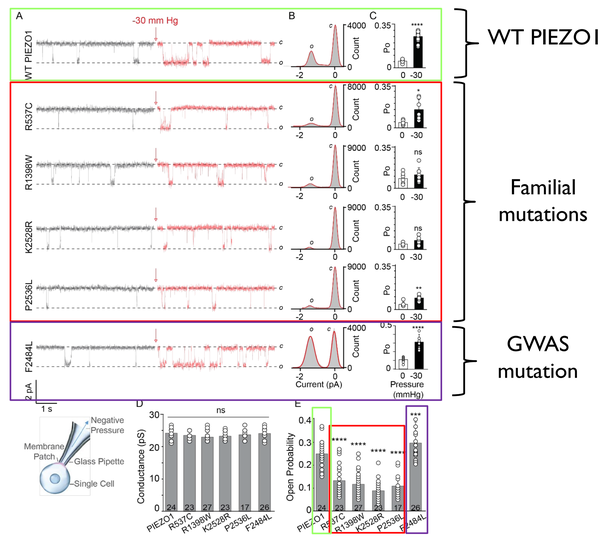


Figure 2. Single-channel currents of WT, familial, and GWAS OA-associated *PIEZO1* Variants. Single-channel current recordings acquired at -60mV, before (red) and after -30 mmHg (grey) pressure pulse. Respective all-point current-amplitude histograms showing the closed (0 pA) and open (-1.5 pA) state of the channel.

Piezo1^{R1398W} differentially effects the transcriptional response of primary human chondrocytes

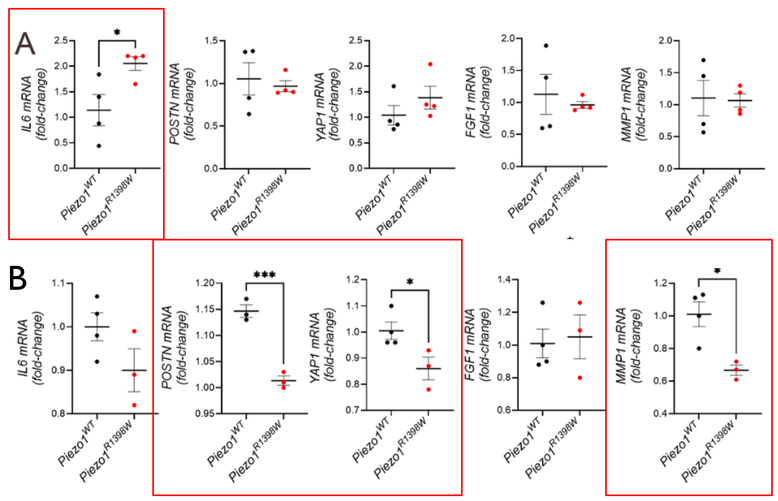


Figure 3. RT-qPCR in primary human chondrocytes electroporated with Piezo1WT or Piezo1^{R1398W}. Gene expression in control chondrocytes **(A)** or chondrocytes treated with IL1β (10ng/ml) for 24 hours **(B)**.

Mice containing the human OA-associated *Piezo1*^{R1398W} allele are protected from PTOA

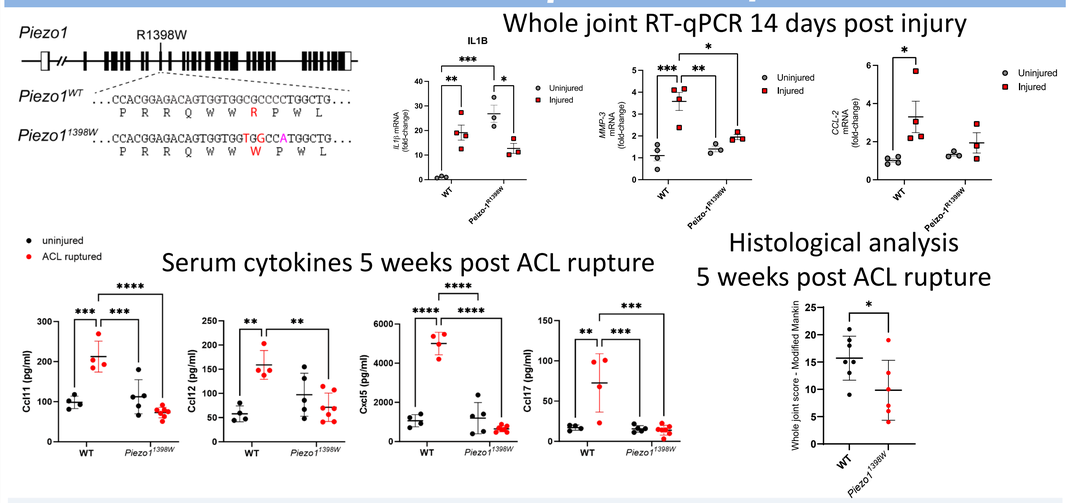


Figure 4. We used CRISPR/Cas9 to generate a mouse that harbors a human OA-associated *PIEZO1*^{R1398W} allele. WT and *PIEZO1*^{R1398W} mice were subjected to ACL rupture and RT-qPCR was performed 14 days post injury and systemic cytokines and whole joint scores were analyzed 5 weeks post injury.

Piezo1^{R1398W} paw synovial fibroblasts have an augmented response to IL1β treatment

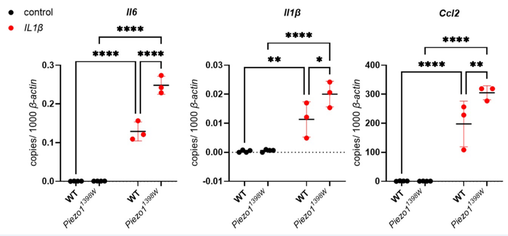
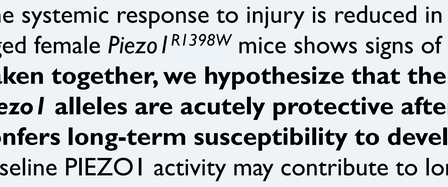


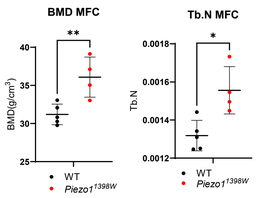
Figure 5. RT-qPCR in primary mouse synovial fibroblasts isolated from WT or Piezo1^{R1398W} mice.

Aged *Piezo1*^{R1398W} female mice appear to have accelerated OA

A 1-year-old *Piezo1*^{1398W} mice have reduced activity



B 2-year-old *Piezo1*^{1398W} mice altered bone properties



C *Piezo1*^{1398W} disrupts signaling pathways in 2-year-old female mice

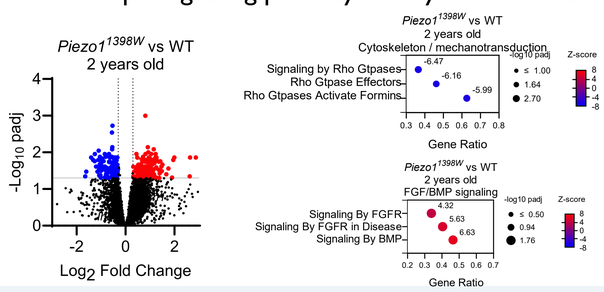


Figure 6. (A) Mouse activity was recorded in 1-year old WT and *Piezo1*^{1398W} mice. **(B)** uCT and **(C)** RNAseq were performed on whole joints isolated from 2-year-old WT and *Piezo1*^{R1398W} mice.

Conclusions

- Familial OA-associated *PIEZO1* alleles show decreased open channel probability, while the GWAS allele appears to increase the open probability.
- Uninjured *Piezo1*^{R1398W} mice express high levels of inflammatory cytokines, which is reduced following injury.
- The systemic response to injury is reduced in *Piezo1*^{R1398W} mice.
- Aged female *Piezo1*^{R1398W} mice shows signs of early onset OA.
- **Taken together, we hypothesize that the hypomorphic *Piezo1* alleles are acutely protective after injury but confers long-term susceptibility to development of OA.**
- Baseline PIEZO1 activity may contribute to long-term maintenance of articular cartilage.

Acknowledgements

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