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Identification of Novel Hedgehog Signaling Pathway Gene Variants Associated With Familial Forms of Osteoarthritis

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Introduction

Osteoarthritis (OA) is a common joint disease characterized by abnormal remodeling of joint tissue, affecting 32.5 million adults in the United States. There is no cure for OA and no therapies prevent disease initiation or progression. We lack effective therapeutics because of our limited understanding of the genes and biological processes underlying or conferring susceptibility to OA. Identifying genetic risk factors is central to understanding the causation of OA and will help guide rational drug design. The **goal** of this study is to identify recurrent novel gene variants that are associated with susceptibility to OA. To do this, we have analyzed the exomes from 150 families with multiple forms of OA and identified candidate gene variants in each family. Here we describe the identification of the Hedgehog (Hh) pathway as a major risk factor for OA susceptibility.

Experimental Design

We used a unique medical genetics resource, the Utah Population Database (https://uofuhealth.utah.edu/huntsman/utah-population-database/), and the University of Utah Orthopaedic Center to identify 150 independent families with dominant inheritance patterns of OA. Within each family, a distinct set of joints are affected, encompassing distal and proximal interphalangeal OA, erosive hand OA, glenohumeral osteoarthritis OA, and 1st metatarsophalangeal (MTP) joint OA. Whole exome sequence (WES) analysis was performed on informative members of families, and rare coding variants that invariably segregated with OA and were predicted to alter gene function were identified.

Results

WES revealed recurrent novel variants in the Hh signaling pathway (**Table 1**). Variants were identified in *SMO* (which encodes Smoothened), *IHH* (which encodes Indian hedgehog), *GLI1* (which encodes Glioma-associated oncogene homolog-1), *GLI3* (which encodes Glioma-associated oncogene homolog-3) genes (**Fig 1**). The *SMO* gene variant allele, identified in a family with erosive hand OA, encodes significant amino acid change (p.Val270Ile) in the G protein receptor, indicating possible alteration to SMO protein function. Similarly, *IHH*, identified in a family with erosive hand OA, and *GLI1*, identified in a family with 1st MTP OA, gene variants encode (p.Gly233Arg) and (p.Pro690Thr), respectively.

The GLI3 gene was found to have two variant alleles, identified in families with interphalangeal joint and 1st MTP OA, encoding (p.Ser297Thr) and (p.Pro1222Ser) in our variant analysis. The two *GLI3* variants are located in separate domains of the protein.

Table 1. *Hedgehog* Signaling Pathway Variants Identified in Independent Osteoarthritis Families

Gene	OA Phenotype (Family)	Variant	Minor Allele Frequency	Protein Domain Affected by Variant
GLI1	1st MTP Joint OA (MTP 23)	c.C2068A:p.P690T	0.000016	NA
GLI3	Finger Interphalangeal Joint OA (FIJ 6)	c.T889A:p.S297T	Novel	NA
GLI3	Erosive Hand OA (ERO 30)	c.C3664T:p.P1222S	0.002656	NA
SMO	Erosive Hand OA (ERO 369)	c.G808A:p.V270I	0.007084	G Protein Receptor Domain
IHH	Erosive Hand OA (ERO 15)	c.G697C:p.G233R	Novel	Intein N-terminal Splicing Motif

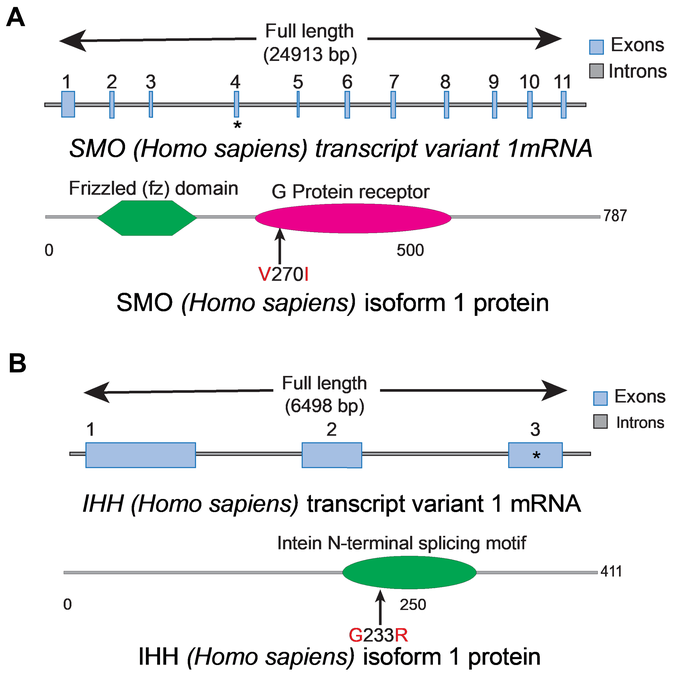
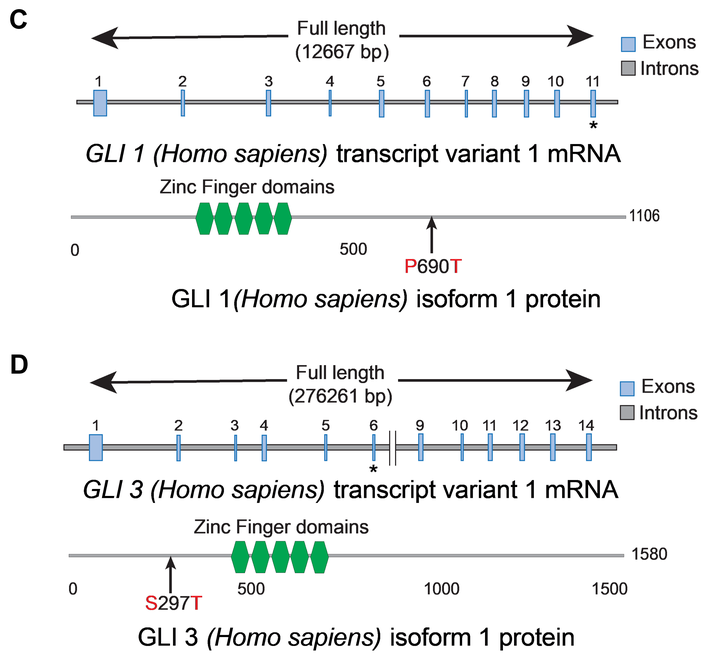


Figure 1: Novel gene variants identified in the Hh signaling pathway. **(A)** Smoothened (*SMO*) **(B)** Indian hedgehog (*IHH*) **(C)** Glioma-associated oncogene homolog 1 (*GLI1*) **(D)** Glioma-associated oncogene homolog 3 (*GLI3*). The top figures indicate genomic structure and asterisks indicate the exon carrying the mutation. The bottom figures depict protein structure with the amino acid change.



Discussion

Gene variants in the Hh pathway are associated with OA susceptibility across a diverse range of joints, suggesting that alterations in Hh signaling is a major risk factor for OA susceptibility.

We are currently analyzing candidate variant functions in human cell lines and zebrafish, and generating mice carrying human disease alleles to understand the contribution of these gene variants to the osteoarthritis phenotype.

We anticipate that identifying these novel gene variants will advance our understanding of OA initiation and progression. This study could provide a scientific basis for establishing new targets for the prevention and treatment of OA.

Acknowledgements

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