Familial Clustering and Genetic Analysis of Severe Thumb Carpometacarpal Joint Osteoarthritis in a Large Statewide Cohort

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Background

Objectives: Our goals were to 1) identify individuals that required surgery for thumb carpometacarpal osteoarthritis (CMCJ OA), 2) determine if CMCJ OA clusters in multigenerational families, 3) define the magnitude of familial risk of CMCJ OA, 4) identify risk factors associated with CMCJ OA, and 5) identify rare genetic variants that segregate with familial CMCJ OA.

Methods: We searched the Utah Population Database to identify a cohort of CMCJ OA patients that required a surgical procedure. Affected individuals were mapped to pedigrees to identify high-risk multigenerational families with excess clustering of CMCJ OA. Cox regression models were used to calculate familial risk of CMCJ OA in related individuals. Risk factors were evaluated using logistic regression models. Whole exome sequencing was used to identify rare coding variants associated with familial CMCJ OA.

Results: We identified 550 pedigrees with excess clustering of severe CMCJ OA. The relative risk of developing CMCJ OA requiring surgical treatment was significantly elevated in first- and third-degree relatives of affected individuals, and significant associations with advanced age, female sex, obesity, and tobacco use were observed. We discovered candidate genes that dominantly segregate with severe CMCJ OA in four independent families, including a rare variant in *Chondroitin Sulfate Synthase 3 (CHSY3)*.

Conclusions: Familial clustering of severe CMCJ OA was observed in a statewide population. Our data indicate that genetic and environmental factors contribute to the disease process, further highlighting the multifactorial nature of the disease. Genomic analyses suggests distinct biological processes are involved in CMCJ OA pathogenesis.

Table 1 - High-Risk Pedigrees with Excess Familial Clustering of Thumb Carpometacarpal Joint Osteoarthritis

Founder Birth Year	Number of Descendants	Number of Affected Individuals	FSIR*
1766	22,460	20	2·1
1740	22,450	24	2·1
1788	16,344	19	2·
1761	11,909	15	3·7
1754	5,105	12	4·1
1788	4,628	8	6·3
1815	1,127	7	7·8
1783	2,228	6	9·1
1809	979	5	12·5
1848	525	4	21·1

* indicates that all FSIR P-values are P < 0·05.

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Table 2 - Increased Familial Risk of Thumb Carpometacarpal Joint Osteoarthritis for both sexes

	N of relatives of CMCJ OA cases	N of relatives of matching controls	P-value	Relative Risk	95% CI Lower Limit	95% CI Upper Limit
Had a 1st degree relative w/ CMC	145	195	0·000	3.62	2.70	4.86
Had a 2nd degree relative w/ CMC	44	167	0.208	1.24	0.89	1.75
Had a 3rd degree relative w/ CMC	207	775	0.048	1.18	1.00	1.39

Table 3 - Age-Specific Incidence Rates of Thumb Carpometacarpal Joint OA by Sex & Female-to-Male Incidence Ratios

	Male		Female		Female-to-male ratio (95% CI)
Age	*N cases*	*Rate Per 10000*	*N cases*	*Rate Per 10000*	
< 20	<11	0·002	0	0	-
20-29	<11	0·003	<11	0·003	1·04 (0·15, 7·41)
30-39	<11	0·016	28	0·058	3·70 (1·69, 8·12)
40-49	57	0·136	235	0·581	4·28 (3·21, 5·72)
50-59	241	0·721	1120	3·370	4·68 (4·07, 5·37)
60-69	466	2·030	1324	5·550	2·73 (2·46, 3·04)
70-79	251	1·860	638	4·170	2·25 (1·94, 2·60)
80-89	46	0·770	108	1·330	1·72 (1·22, 2·43)
90+	<11	0·321	<11	0·057	0·18 (0·02, 1·71)

Table 4 – CMCJ OA Risk Factors using Conditional Logistic Regression Models Adjusting for Diabetes

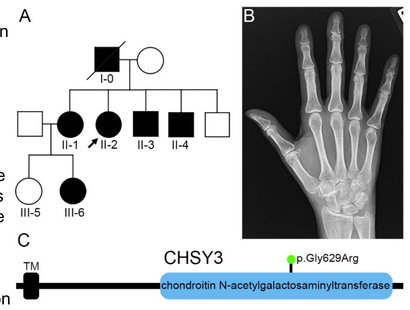
Males	P-value	Relative Risk	95% CI Lower Limit	95% CI Upper Limit
Ever diagnosed with alcoholism	0.173	0.81	0.59	1.10
Ever diagnosed with diabetes	0.402	1.07	0.92	1.25
Ever diagnosed with obesity	**0.000**	**1.59**	**1.36**	**1.86**
Ever diagnosed with tobacco	**0.000**	**1.33**	**1.15**	**1.53**
Had at least one 1st degree relative with CMCJ OA	**0.000**	**3.78**	**2.42**	**5.89**
Had at least one 3rd degree relative with CMCJ OA	**0·003**	**1.58**	**1.15**	**2.18**
Females	**P-value**	**Relative Risk**	**95% CI Lower Limit**	**95% CI Upper Limit**
Ever diagnosed with alcoholism	0·454	1·09	0·87	1·35
Ever diagnosed with diabetes	0·175	0·94	0·85	1·03
Ever diagnosed with obesity	**0·000**	**1·24**	**1·14**	**1·36**
Ever diagnosed with tobacco	**0·000**	**1·45**	**1·33**	**1·58**
Had at least one 1st degree relative with CMCJ OA	**0·000**	**3·21**	**2·46**	**4·19**
Had at least one 3rd degree relative with CMCJ OA	0.722	1.04	0.85	1.26

Table 5 – Candidate variant genes found in high-risk thumb CMCJ OA pedigrees

Family	OA Phenotypes and Individuals Analyzed	Candidate Gene(s) *Polyphen/SIFT Prediction	SkeletalVis Expression Acc.No./Tissue
CMC4	5 affected; one unaffected (Pedigree in Figure 1)	CHSY3 – NM_175856: exon3:c.G1885A:p.G629R*	22659600 Human cartilage
CMC1	Two affected sisters.	B4GALNT2 -NM_001159387: exon3:c.G323T:p.R108I*	GSE74220 Human cartilage
		LTF -NM_001199149: exon16:c.C1898T:p.T633I*	GSE51588 Human bone
CMC3	Four affected siblings	STAT4 - NM_001243835: exon2:c.A125G:p.D42G*	GSE10575 Human cartilage
		TRPM3 - NM_001007471: exon10:c.C1358T:p.S453L*	E-MTAB-6266_B Human cartilage
CMC743	Two affected; two unaffected	MERTK - NM_006343: exon5:c.C791G:p.A264G*	E-MTAB-6266_B Human cartilage
		DOK3 - NM_001144875: exon3:c.C193T:p.R65W *	GSE51588 Human bone

*Polyphen - probably_damaging; SIFT – deleterious

Figure 1 – *A dominant CHSY3 mutation segregates with thumb carpometacarpal joint osteoarthritis.*
(A) CMC4 pedigree. Severe CMCJ OA segregates as an apparent autosomal dominant trait. Arrow marks the proband (II-2). The founder (deceased, I-0) was not genotyped, but had a medical history of CMCJ OA. Exomes were sequenced from two generations of the family (individuals II-1-4 and III-5 and 6). All affected individuals genotyped (II-1-4 and III-6) were heterozygous for the rare variant (rs145272862) and the unaffected individual (III-5) genotyped was homozygous for the reference allele. (B) Right hand radiograph of the proband demonstrating CMCJ OA. (C) Schematic diagram of the CHSY3 protein indicating the transmembrane domain (TM) and the chondroitin N-acetylgalactosaminyltransferase domain and the location of the p.Gly629Arg mutation in the catalytic domain.



Conclusions

In this study, we leveraged a unique statewide medical genetics resource, the UPDB, to identify a cohort of individuals diagnosed with severe CMCJ OA. Our study focuses on a unique population of CMCJ OA individuals; those with symptoms severe enough to require surgical management of symptoms (CMC fusion or arthroplasty). From this cohort of individuals with severe CMCJ OA we have i) identified 550 unrelated high-risk pedigrees demonstrating familial enrichment severe CMCJ OA, ii) determined that first- and third-degree relatives of an individual with severe CMCJ OA is at approximately 3·62-fold and 1·18-fold increased risk of developing the disease, respectively, iii) determined that age, sex, obesity, tobacco-use, and having a first- or third-degree relative with severe CMCJ OA are significant risk factors associated with the disease, and iv) and identified rare, dominantly segregating coding variants in four CMCJ OA pedigrees. In sum, these data suggest that both genetic and physiological factors contribute to the development of severe CMCJ OA in a large population-based cohort.