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Haemochromatosis *HFE* genotypes and association with chondrocalcinosis: Early data from analysis in UK Biobank

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Introduction

The iron-overload disorder haemochromatosis is primarily caused by the homozygous *HFE* p.C282Y variant. Musculoskeletal impacts have been associated with haemochromatosis and with the p.C282Y homozygous mutation. These are particularly noted in males who have increased risk of joint replacement surgeries, [1,2] osteoporosis and fracture.[3,4]

The arthritis of haemochromatosis is also well-recognised [5] and typically affects the weight bearing joints, with chondrocalcinosis a recognised associated feature (See Figures 1 & 2).

Aim

While arthropathy and chondrocalcinosis are well-recognised features of the clinical disease, less is known about chondrocalcinosis formation in p.C282Y homozygotes.
We used UK Biobank images to assess for chondrocalcinosis in the knee and to explore any association with p.C282Y genotype.

Chondrocalcinosis

Chondrocalcinosis is a descriptive term used to describe the presence of calcium deposition within articular cartilage (see Fig 2).

It is often associated with haemochromatosis although there is wide variation in the frequency at which it is reported, with estimates ranging from 5 to 49%.[6,7]

Method

Resources: iDXA (GE-Lunar, Madison, WI, USA) images acquired from UK Biobank* were used

Participants: Data from European ancestry participants; p.C282Y homozygotes and controls (aged 48-80years) matched for age, sex, and BMI.

Image analysis: 264 Posteroanterior (PA) DXA scans of both knees (Fig.1) were reviewed for radiological evidence of chondrocalcinosis by an experienced reporting radiographer, blind to case/control.

Statistical Analysis: Logistic regression models were carried out in STATA 18 using a matched analysis.

Fig. 1

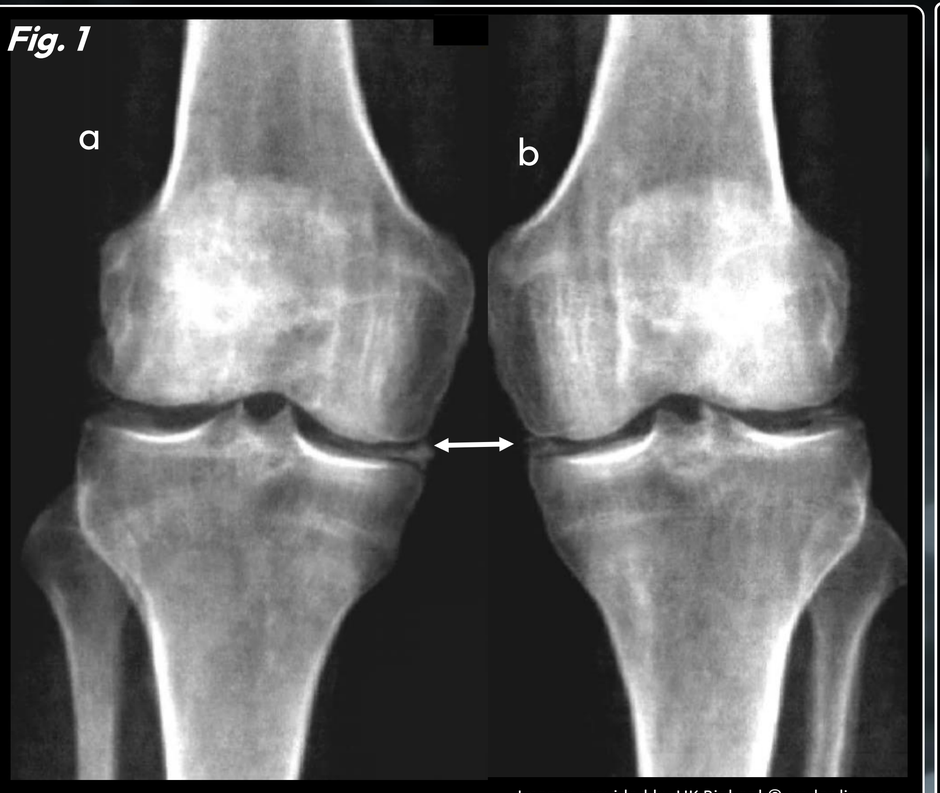

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Fig.1 Meniscal Chondrocalcinosis.
iDXA images of right (a) and left (b) knees showing calcification of cartilage (chondrocalcinosis [white arrows]) in the tibiofemoral joint spaces of the knees of a male p.C282Y homozygote.

Fig.2

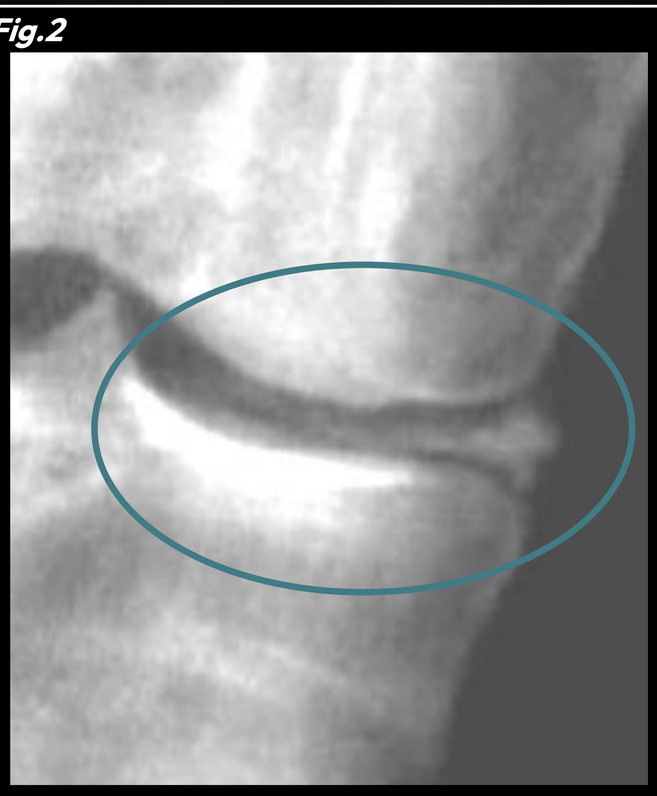

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Fig.2 Close up of chondrocalcinosis (circled) seen in the medial compartment of Fig.1 (a)

Results

- Only one (male) homozygote with chondrocalcinosis had received a confirmed haemochromatosis diagnosis.
- The incidence of radiologically evident chondrocalcinosis in the tibiofemoral joint space was higher in both male and females when compared to those with no *HFE* mutations (Table 1).
- Logistic regression demonstrated significantly increased odds of chondrocalcinosis in male p.C282Y homozygotes (in either imaged knee) when compared with matched controls without *HFE* haemochromatosis mutations
- Female p.C282Y homozygotes did not have increased odds of chondrocalcinosis in either knee.

Table 1: Results of image evaluation by sex and by *HFE* genetic status

		Number of participant Images	Chondrocalcinosis (%)	OR	p Value	95% CI
Male	**no *HFE* mutations**	50	1 (2.00)	1.0	-	-
	p.C282Y Homozygotes	52	10 (19.23)	11.67	0.025	1.35 – 100.66
Female	**no *HFE* mutations**	78	2 (2.56)	1.0	-	-
	p.C282Y Homozygotes	84	7 (8.33)	3.45	0.134	0.68 – 17.51
Male and Female, no *HFE* mutations		128	3 (2.34)	1.0	-	-
Male and Female, p.C282Y Homozygotes		136	17 (12.50)	5.95	0.005	1.70 – 20.83

Conclusion

- In this community genotyped sample, both male and female p.C282Y homozygotes demonstrated increased incidence of chondrocalcinosis within the tibiofemoral joint space when compared to those with no *HFE* hemochromatosis genetic mutations.
- The incidence of chondrocalcinosis in male homozygotes was more than double that of the female homozygotes
- Larger sample sizes are needed to increase power and we plan to review further iDXA images within UK Biobank, and to examine for associations with an arthritis diagnosis and relative pain scores.
- These results may support further investigations such as serum ferritin levels when chondrocalcinosis is identified on imaging.

References:

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***UK Biobank**

UK Biobank is a large-scale biomedical database and research resource containing de-identified genetic, lifestyle and health information and biological samples from ~500,000 participants aged 40 to 70 years (mean 56.8years). Participants gave informed consent for genotyping and data linkage to medical records.

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