Increased burden of common risk alleles in children with a significant fracture history

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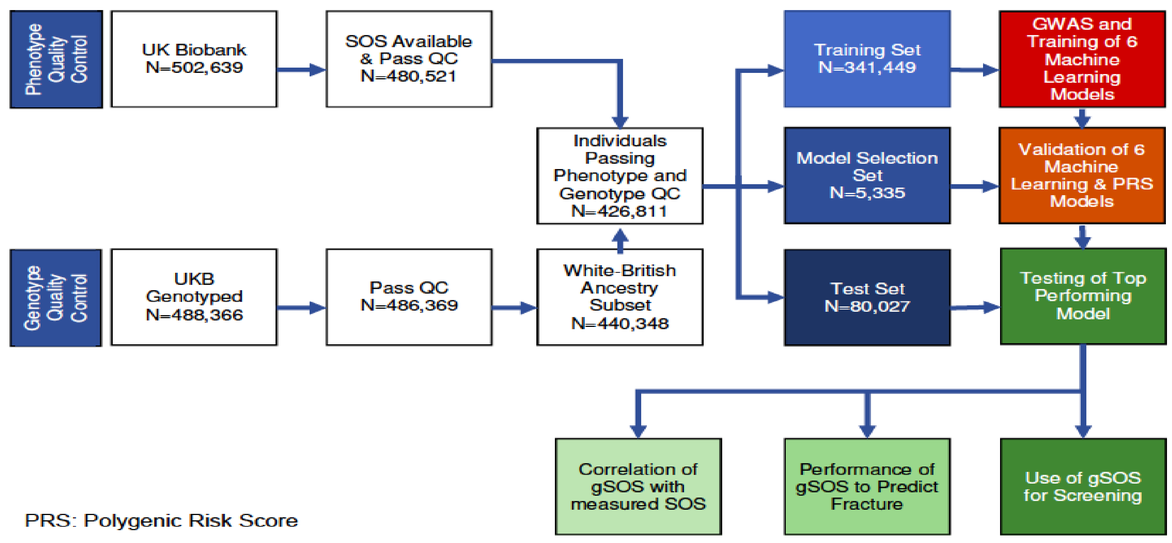
Background

•Fractures are common in children, but a significant fracture history, defined as low-trauma vertebral fractures or multiple long bone fractures, is rare.
•Children with such history and no osteogenesis imperfecta (OI) are often presumed to have another Mendelian disease.
•However, in adults, multiple common risk alleles of small effect influence risk of fracture.
•We tested if subjects with a significant childhood fracture history have an increased burden of risk alleles.
•To do so, we applied a polygenic risk score (gSOS) which predicts osteoporotic fracture, in a cohort of subjects with significant fracture history in childhood and no identified OI.

Methods

Figure 1: Development of a polygenic risk score for osteoporotic fracture (gSOS) from heel ultrasound (Forgetta et al, Biorxiv 2018).



Results

a. *3 cohorts with significant fracture history*

Table 1: Demographics of the 3 cohorts.

	Canadian cohort	Finnish cohort 'fracture prone'	Finnish cohort 'primary osteoporosis'
N	60	53	18
Age (median/range)	11.4(1-21.2)	10.3(4.3-16.8)	-
Women	22 (37%)	16(30%)	-
zBMD (mean/sd)	-1.82(1.3)	-0.46(1.0)	-1.84(1.34)
Vertebral fracture: yes	11 (18%)	14(26%)	13(72%)
Any long bone fracture: yes	54(90%)	49(92%)	16(89%)
Long bone fracture (median/range)	2.5(0-12)	3(0-7)	2(0-7)

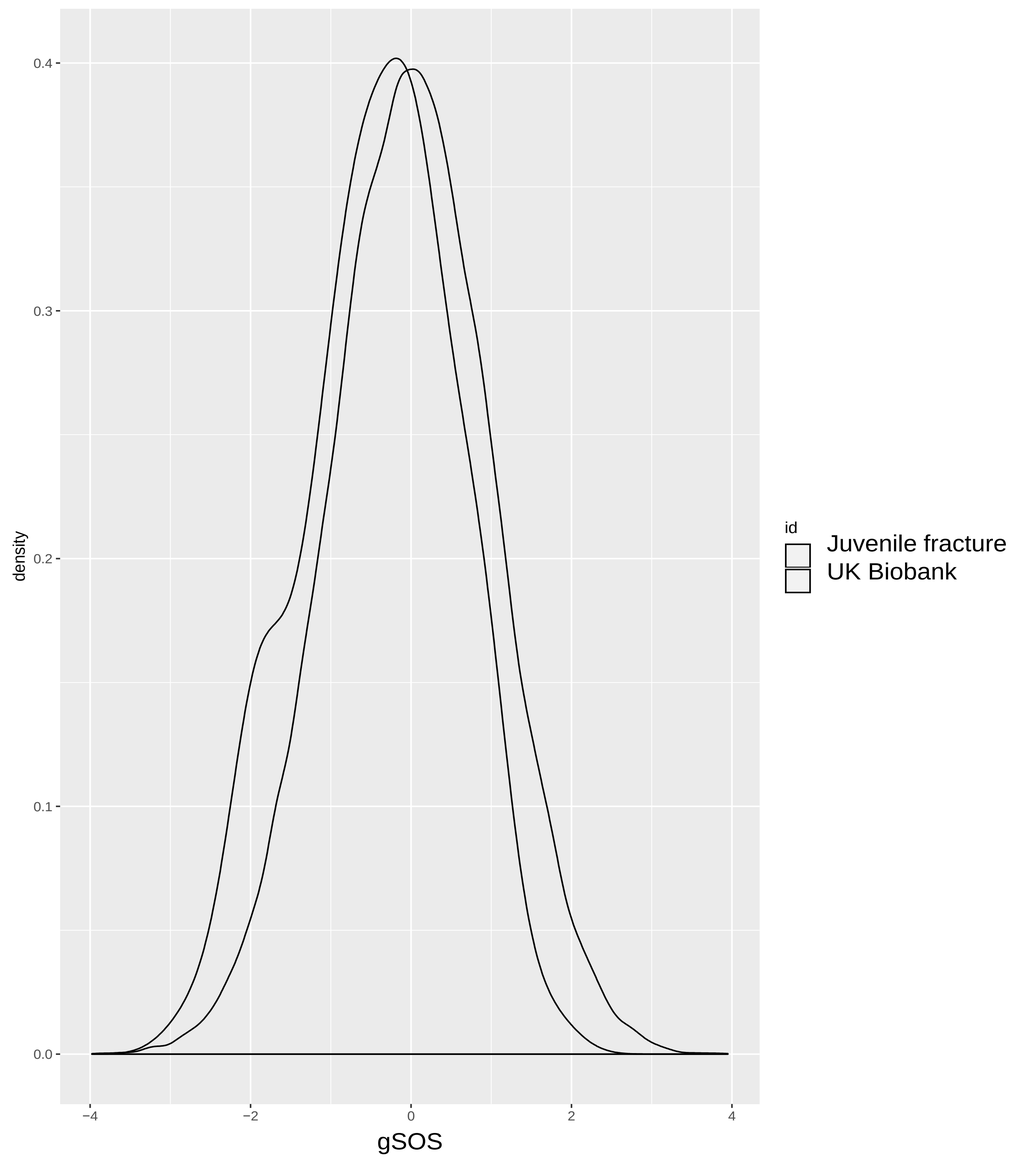
b. *Results: gSOS estimates and comparison to UK Biobank*

Table 2: Results of the main analysis in the entire juvenile fracture cohort and of the sensitivity analyses in subsets of the main cohort.

	gSOS	p-value for comparison with UK Biobank
Main analysis		
All 'juvenile fracture' (n=131)	-0.47 (1.05)	1.1×10^{-5}
UK Biobank (n=80,027)	0.00 (1.00)	-
Sensitivity analyses in subsets of the main cohort		
Canadian cohort (n=60)	-0.82 (0.92)	3.7×10^{-9}
Finnish 'primary osteoporosis' cohort (n=18)	-0.54 (1.01)	0.04
Finnish 'fracture prone' cohort (n=53)	-0.04(1.06)	0.77
'Suspicion of monogenic disease'(n=78)	-0.76(0.94)	5.3×10^{-10}

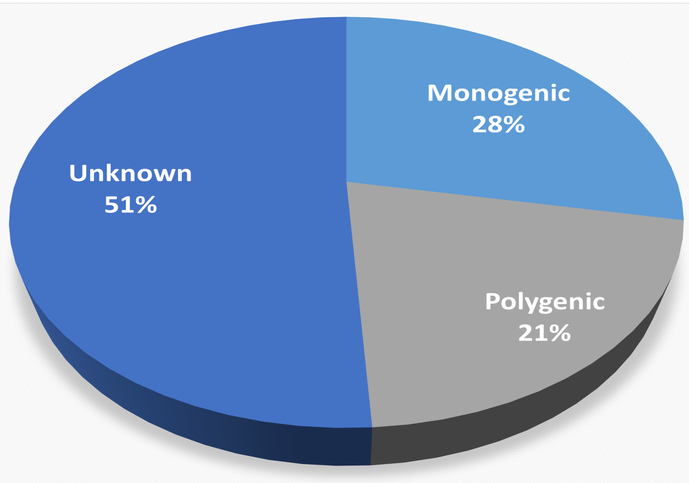
c. *Distribution of gSOS :juvenile fracture cohort vs UK Biobank*

Figure 3: Distribution of gSOS in 131 individuals of the juvenile fracture cohort (pink) and in 80,027 subjects from UK Biobank (blue).



d. *Monogenic vs polygenic etiology of significant fracture history*

Figure 4: Among 108 individuals who underwent panel sequencing for OI genes, percentage of those with a gSOS below the mean in excess to what we would expect by chance alone, and of those with an identified OI-related mutation.



Conclusions

- We provide evidence for a polygenic etiology of fractures in children with significant fracture history and no OI.
- Patients with clinically-apparent Mendelian disease referred to specialists might have a burden of common risk alleles which could influence their risk of fracture.