A Whole-Genome Sequencing Association Study of Low Bone Mineral Density Identifies New Susceptibility Loci in the Phase I Qatar Biobank Cohort

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ABSTRACT

Bone density disorders are characterized by a reduction in bone mass density and strength, which lead to an increase in the susceptibility to sudden and unexpected fractures. Despite the serious consequences of low bone mineral density (BMD) and its significant impact on human health, most affected individuals may not know that they have the disease because it is asymptomatic. Therefore, understanding the genetic basis of low BMD and osteoporosis is essential to fully elucidate its pathobiology and devise preventative or therapeutic approaches. Here we sequenced the whole genomes of 3000 individuals from the Qatar Biobank and conducted genome-wide association analyses to identify genetic risk factors associated with low BMD in the Qatari population. Fifteen variants were significantly associated with total body BMD ($p < 5 \times 10^{-8}$). Of these, five variants had previously been reported by and were directionally consistent with previous genome-wide association study data. Ten variants were new: six intronic variants located at six gene loci (MALAT1/TALAM1, FASLG, LSAMP, SAG, FAM189A2, and LOC101928063) and four intergenic variants. This first such study in Qatar provides a new insight into the genetic architecture of low BMD in the Qatari population. Nevertheless, more studies are needed to validate these findings and to elucidate the functional effects of these variants on low BMD and bone fracture susceptibility.
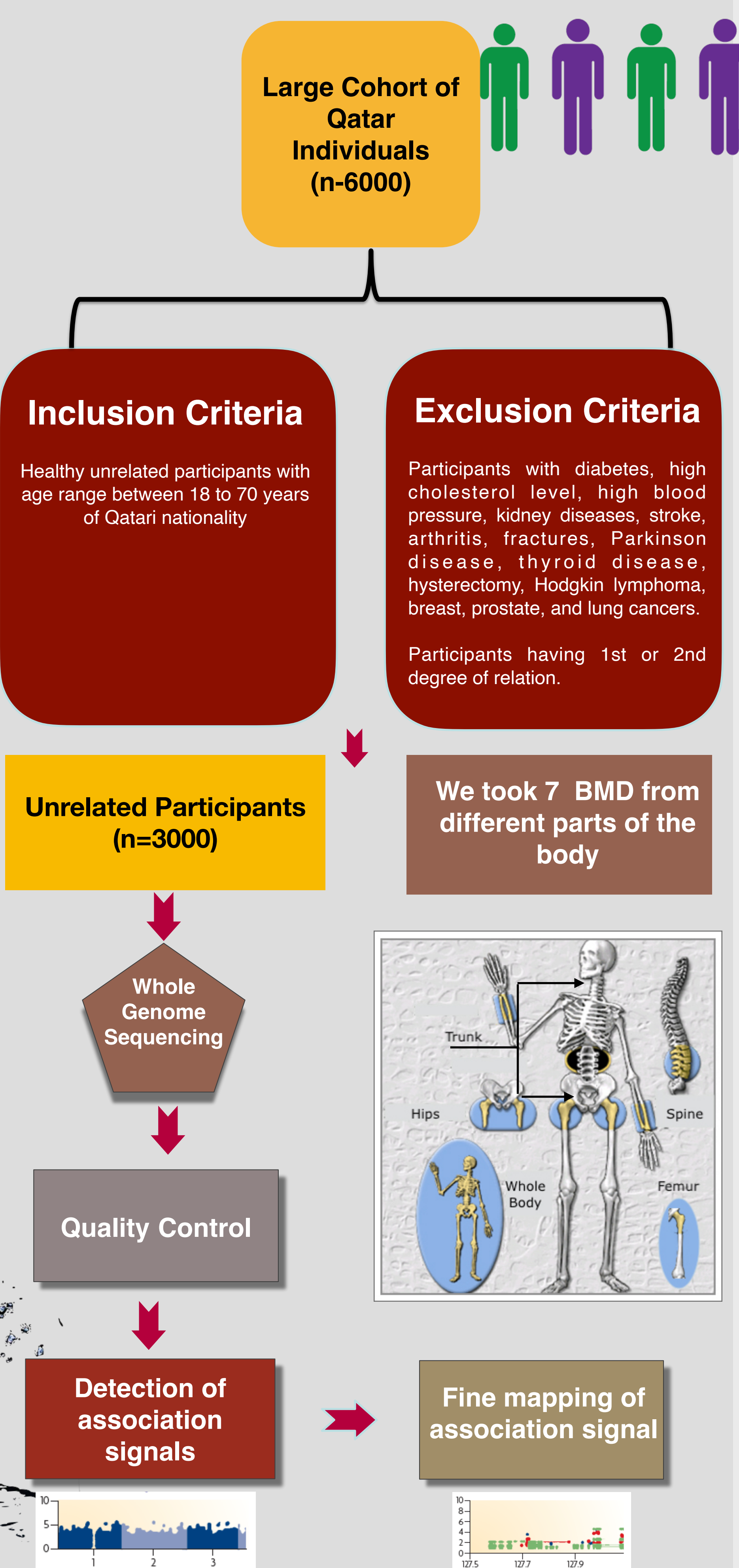
Introduction

Osteoporosis is a common disease characterized by an increased propensity to fracture owing to decreased bone mass and bone quality. Osteoporosis is a global public health problem affecting over 200 million people worldwide.according to WHO. Osteoporosis is diagnosed by a bone mineral density test (BMD). BMD is most commonly performed using dual-energy x-ray absorptiometry (DEXA) or bone densitometry. GWAS is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease.

AIMS

The aim of our study is to evaluate the role of genetic factors in the pathogenesis of osteoporosis, thereby discovering new genetic loci and the biological pathways, which may help identify drug targets for the prevention and treatment of fragility fracture.
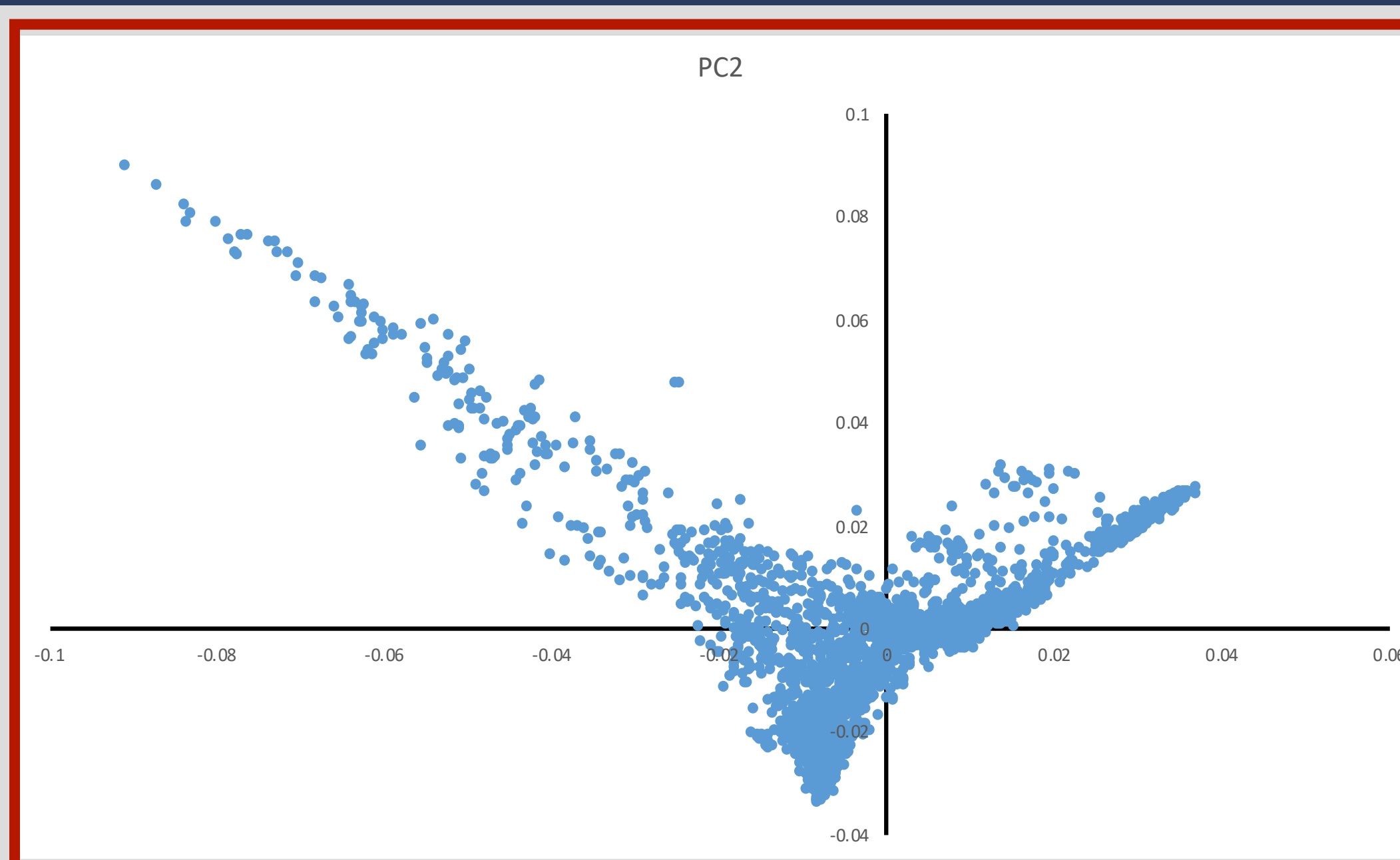
METHODS AND MATERIALS

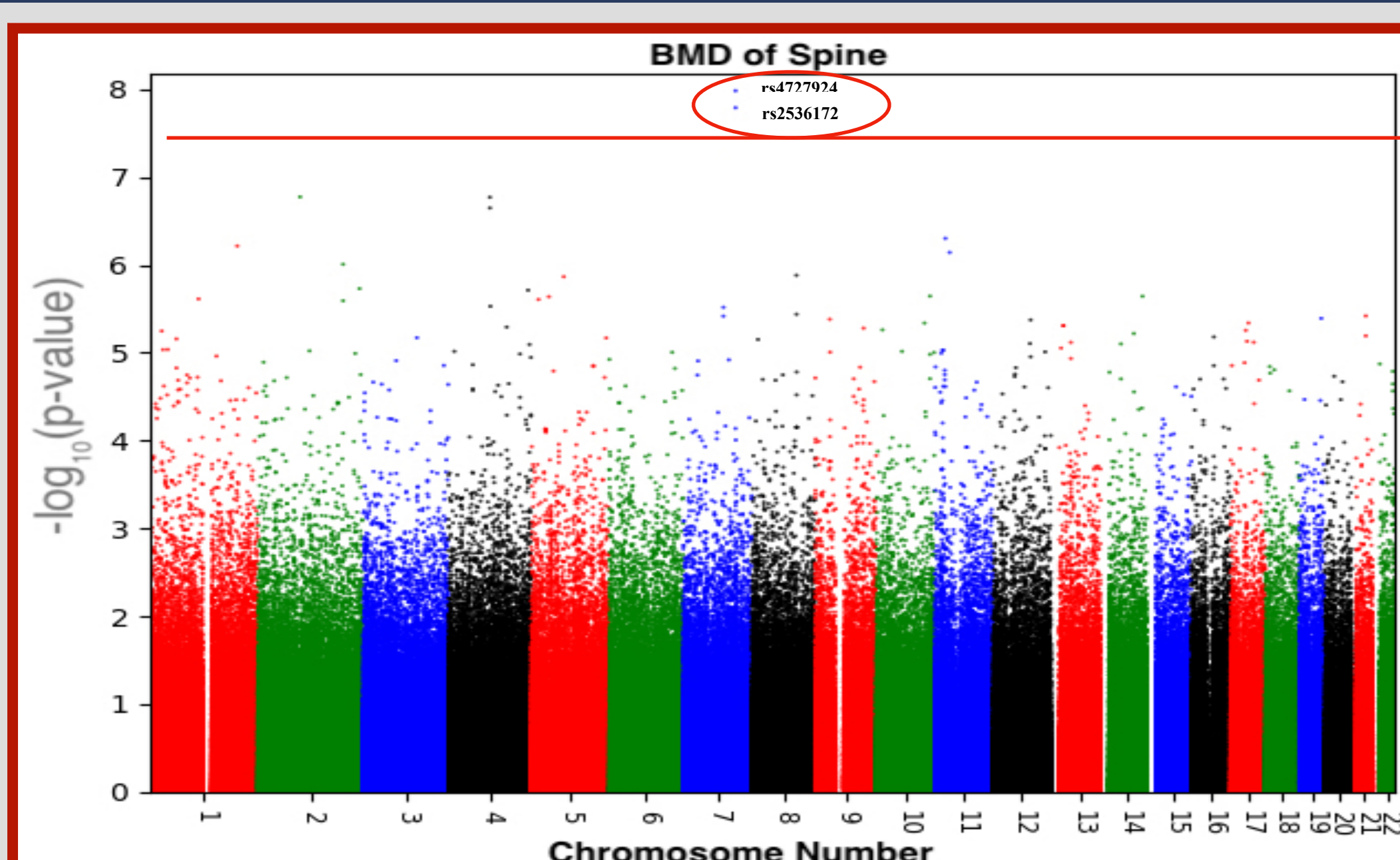Large Cohort of Qatar Individuals (n-6000)

Inclusion Criteria
Healthy unrelated participants with age range between 18 to 70 years of Qatari nationality

Exclusion Criteria
Participants with diabetes, high cholesterol level, high blood pressure, kidney diseases, stroke, arthritis, fractures, Parkinson disease, thyroid disease, hysterectomy, Hodgkin lymphoma, breast, prostate, and lung cancers.
Participants having 1st or 2nd degree of relation.

Unrelated Participants (n=3000)

We took 7 BMD from different parts of the body

Whole Genome Sequencing

Quality Control

Detection of association signals → Fine mapping of association signal

RESULTS & DISCUSSION

Demographic data of the Cohort

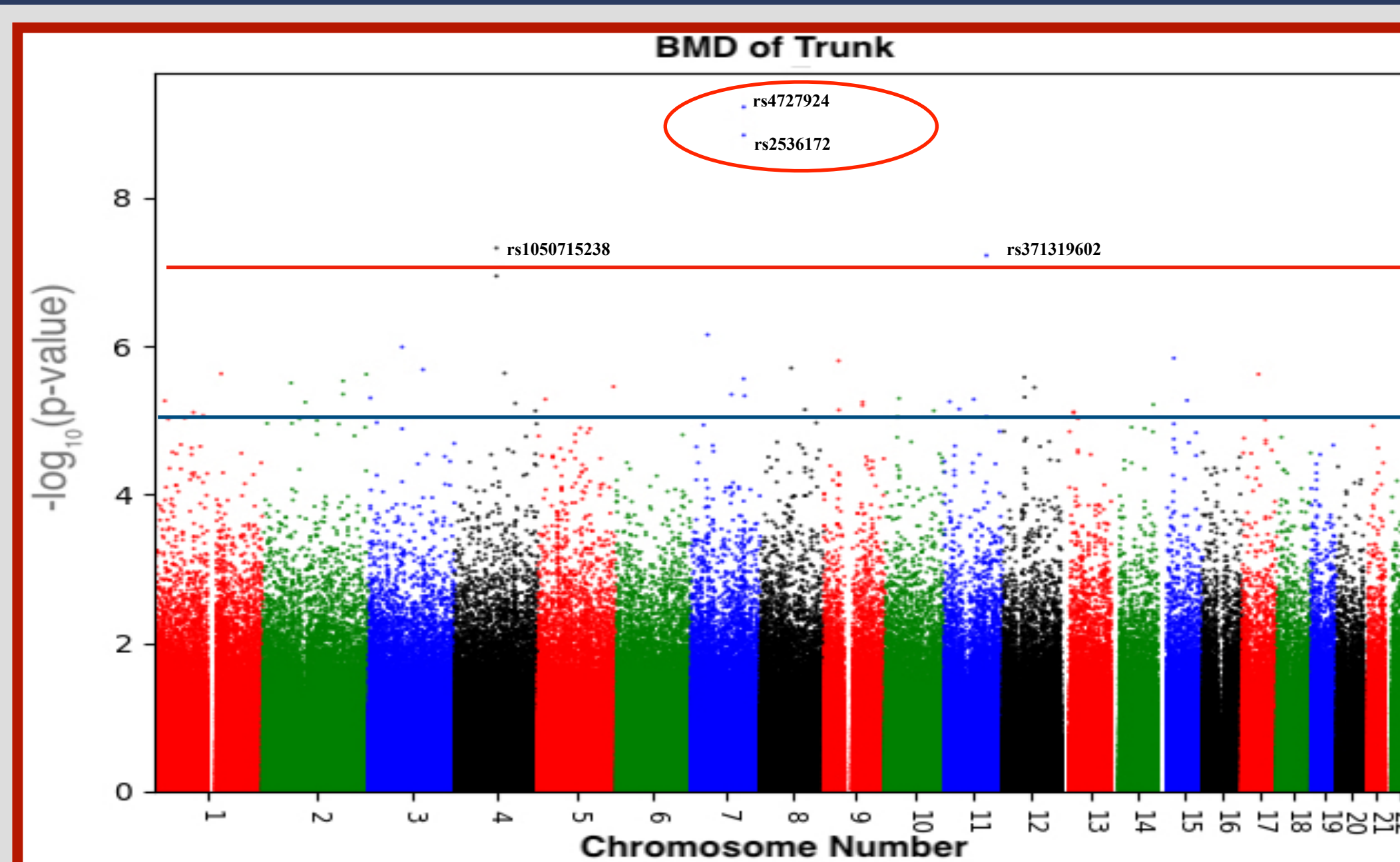| Parameter	Male	Female	P-Value
Number of participants	1442	1558	
Age (years)	36.59 (±10.6)	36.19 (±11.6)	0.329
Height (cm)	172.37 (±6.3)	158.09 (±5.9)	0
Weight (kg)	84.84 (±17.9)	71.18 (±15.9)	0
BMI	28.29 (±5.4)	28.48 (±6.2)	0.391

Qatari Population consist of 3 subpopulation

14 SNPs Significantly Associated with Whole Body
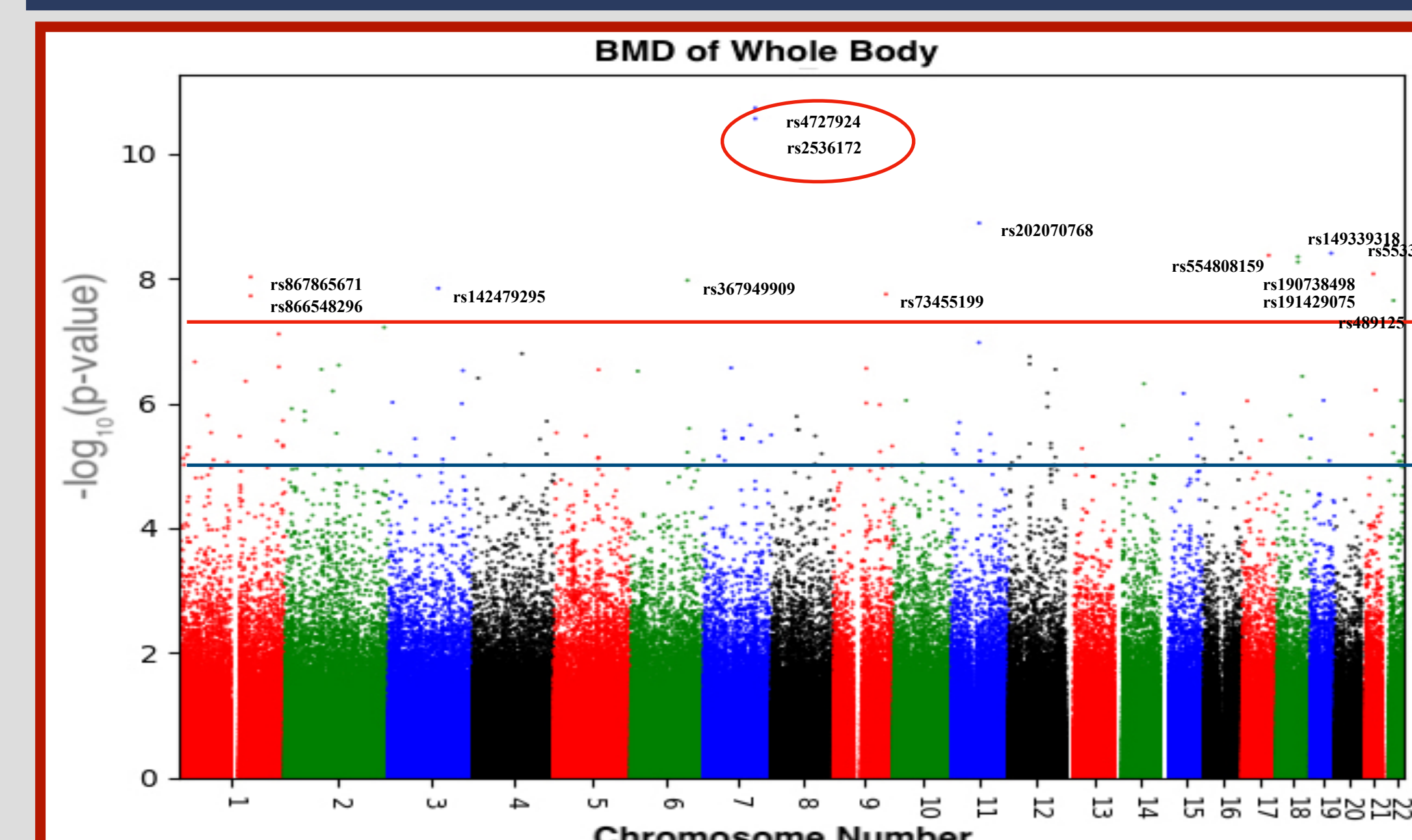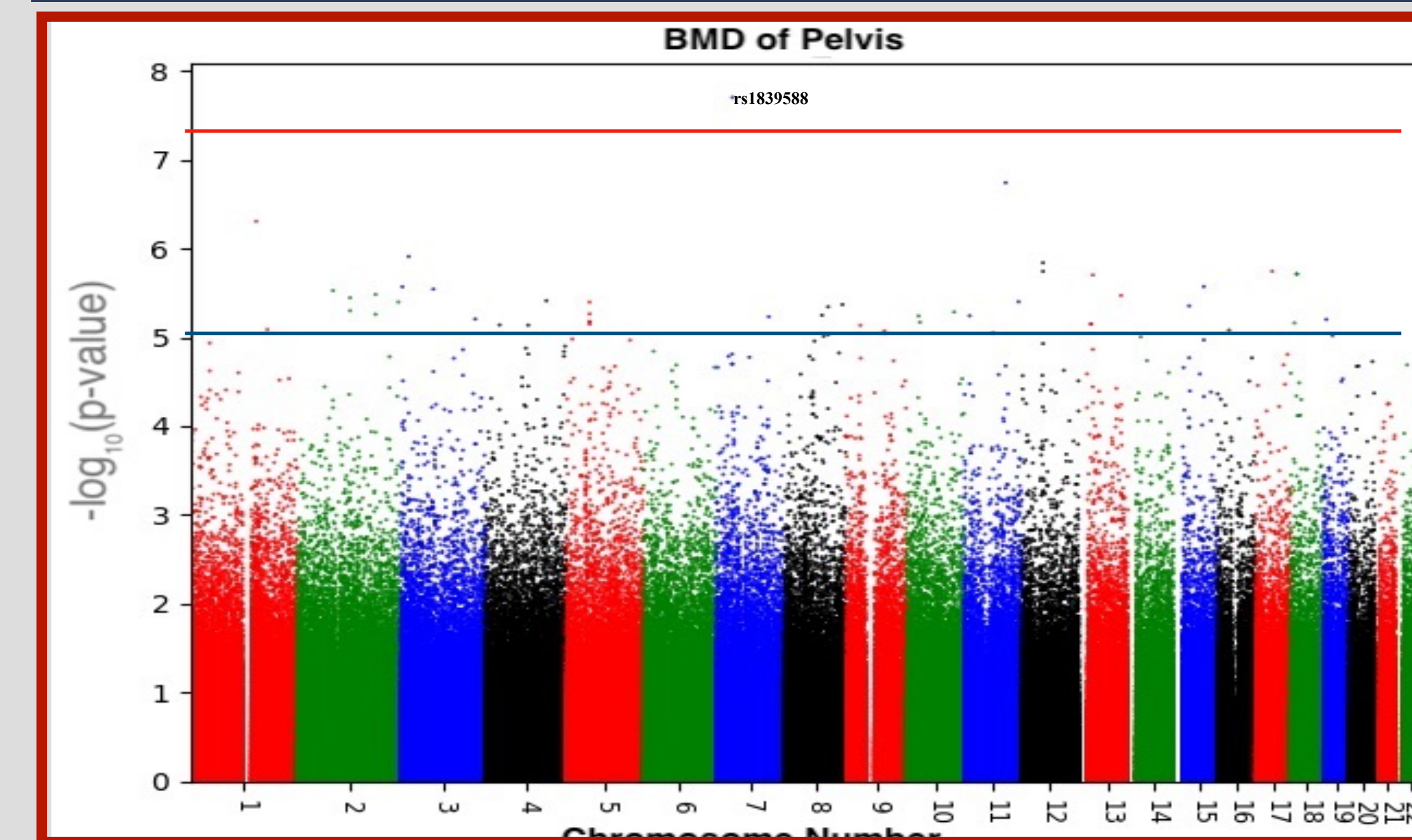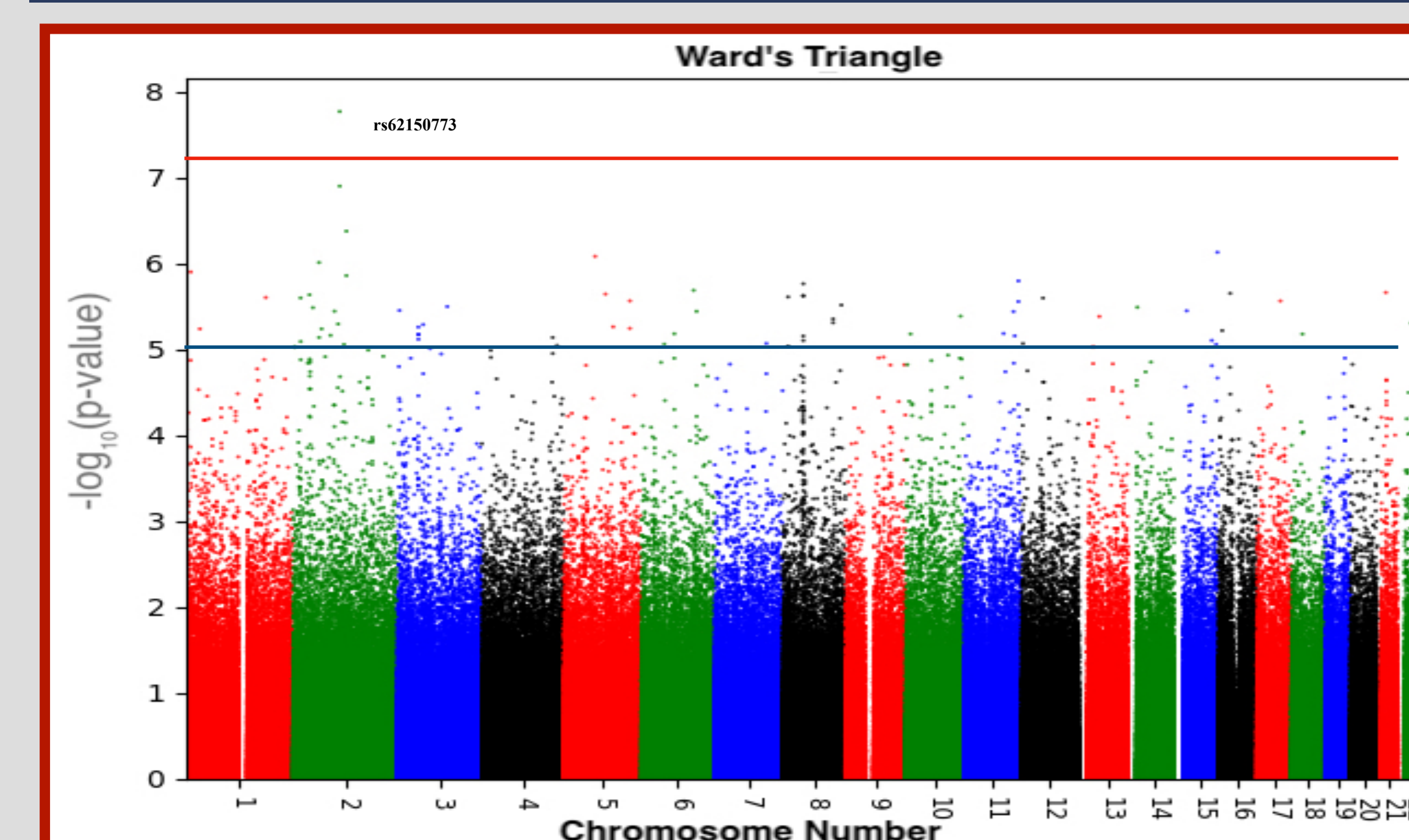
2 SNPs Significantly Associated with Spine BMD

1 SNP Significantly Associated with Pelvis BMD

4 SNPs Significantly Associated with Trunk BMD

1 SNP Significantly Associated with Femoral Ward

Conclusion

- We are the first GWA study to include 7 BMD measurements from different parts of the body
- 18 SNPs were identified to be associated with Osteoporosis in the Qatari Population
- 6 SNPs were replicated from UK Biobank GEFOS
- The 2 most significant SNPs were identified on chromosome 7q31.31 at genome wide significance level $p \le 1.86 \times 10^{-11}$ and were identified in BMD of whole body, spine and trunk
- 12 Novel SNPs were identified in our study

Acknowledgements