Supplementary Information

Microbial Influences on Calcium-Phosphorus Homeostasis and Metabolic Bone Diseases: A Bidirectional Mendelian Randomization Study on the Gut-Bone Axis

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Figures S1. Leave-one-out plots of significant and nominally significant estimates of genetically predicted gut microbiota on osteoporosis;

Figures S2. Leave-one-out plots of significant and nominally significant estimates of genetically predicted gut microbiota on osteopenia;

Figures S3. Leave-one-out plots of significant and nominally significant estimates of genetically predicted gut microbiota on osteonecrosis;

Figures S4. Leave-one-out plots of significant and nominally significant estimates of genetically predicted gut microbiota on osteomyelitis;

Figures S5. Leave-one-out plots of significant and nominally significant estimates of genetically predicted gut microbiota on hypoparathyroidism;

Figures S6. Leave-one-out plots of significant and nominally significant estimates of genetically predicted gut microbiota on hyperparathyroidism;

Figures S7. Scatterplot of genetically predicted gut microbiota on osteoporosis;

Figures S8. Scatterplot of genetically predicted gut microbiota on osteopenia;

Figures S9. Scatterplot of genetically predicted gut microbiota on osteonecrosis;

Figures S10. Scatterplot of genetically predicted gut microbiota on osteomyelitis;

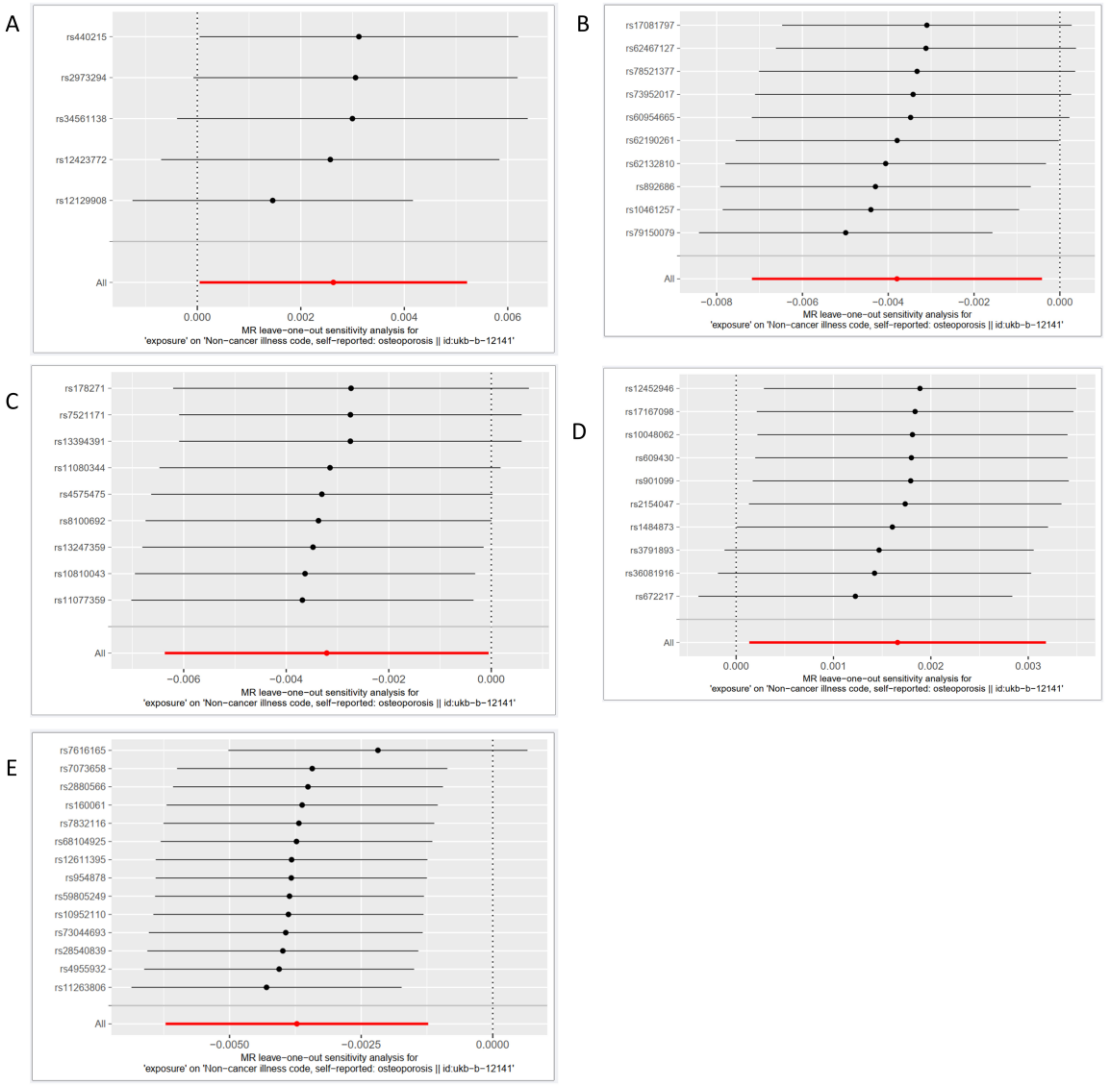
Figures S11. Scatterplot of genetically predicted gut microbiota on hypoparathyroidism;

Figures S12. Scatterplot of genetically predicted gut microbiota on hyperparathyroidism;

Figures S13. LocusZoom and LocusCompare plots of significant and nominal significant estimates from genetically predicted gut microbiota on six metabolic bone diseases.

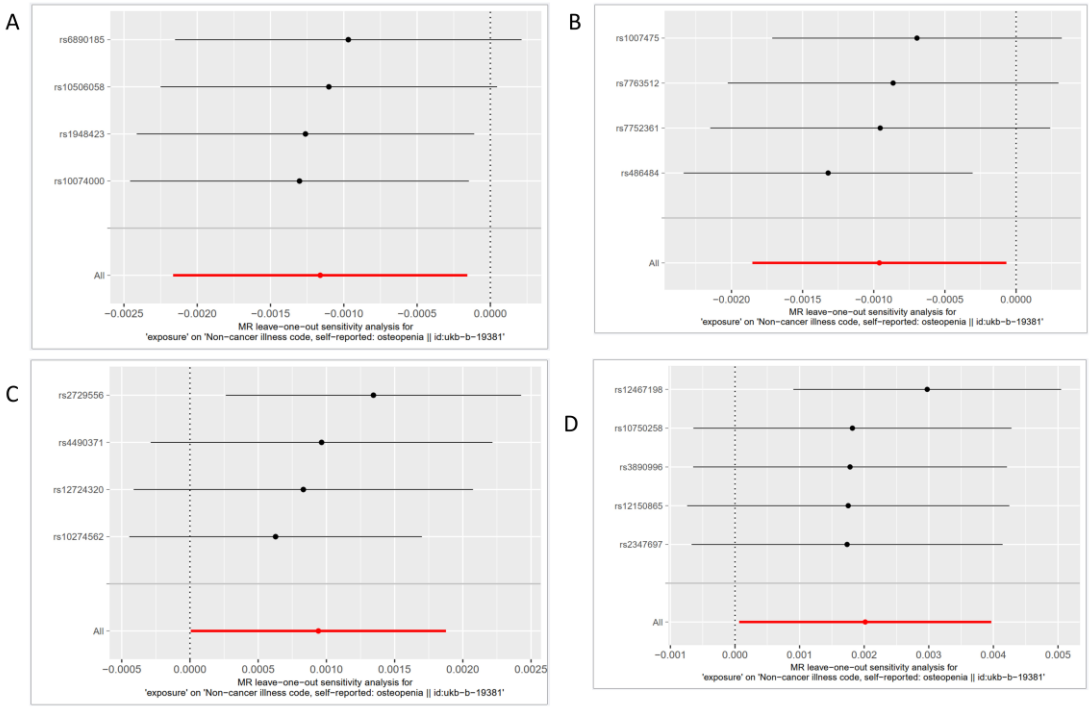
Supplement Figure S1

Leave-one-out plots of significant and nominal significant estimates from genetically predicted gut microbiota {(A)genus..Eubacteriumoxidoreducens;(B)genus.ChristensenellaceaeR.7;(C)genus.Coprococcus3;(D)genus.Howardella;(E) genus.LachnospiraceaeNK4A136} on Osteoporosis



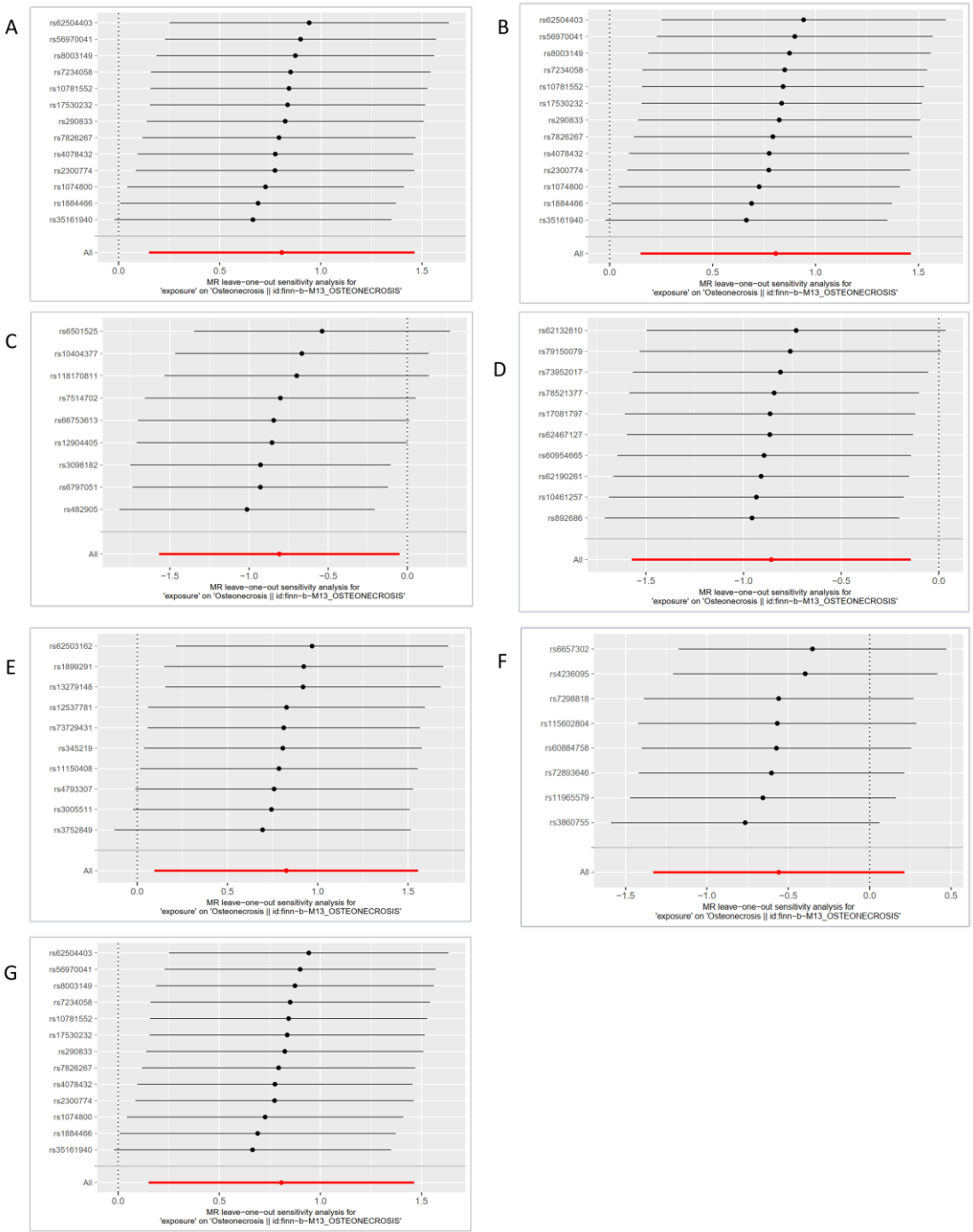
Supplement Figure S2

Leave-one-out plots of significant and nominal significant estimates from genetically predicted gut microbiota {genus..Clostridiuminnocuum;(B)genus.Butyrivibrio;(C)genus.RuminococcaceaeUCG011;(D)phylum.Proteobacteria} on Osteopenia



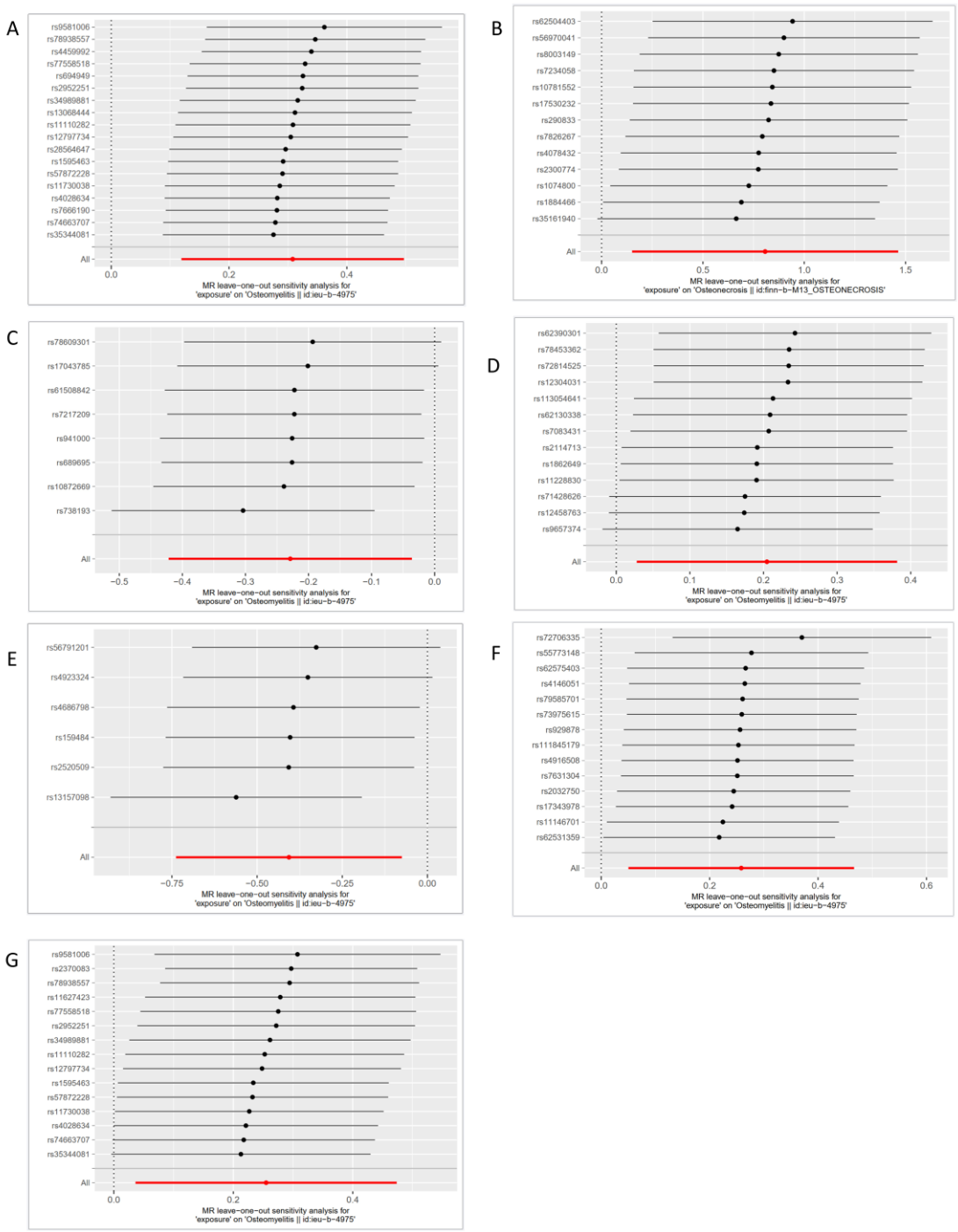
Supplement Figure S3

Leave-one-out plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)class.Erysipelotrichia;(B)family.Erysipelotrichaceae;(C)family.Family XIII;(D)genus.ChristensenellaceaeR.7;(E)genus.Dorea;(F)genus.Parabacteroides;(G)order.Erysipelotrichales} on Osteonecrosis



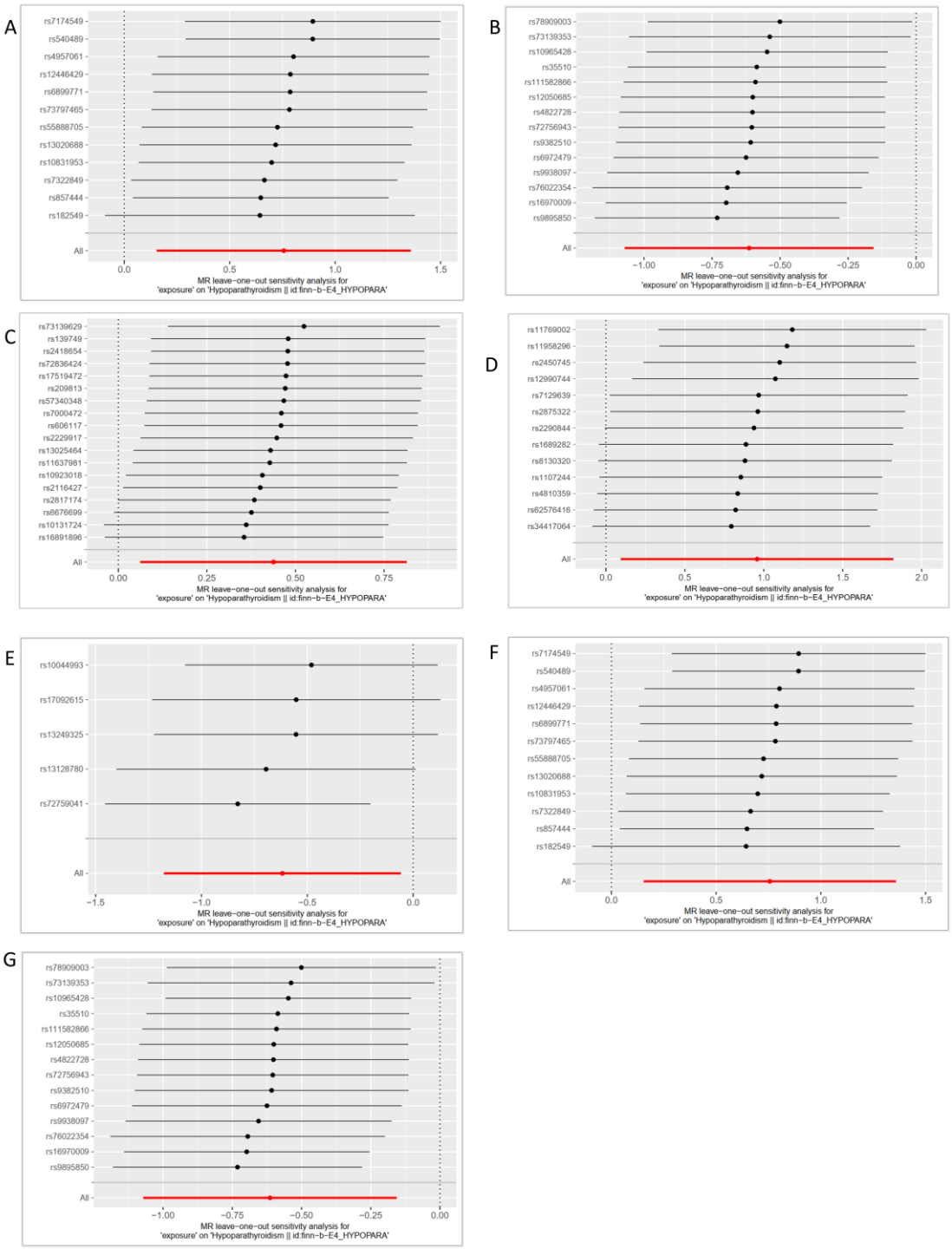
Supplement Figure S4

Leave-one-out plots of significant and nominal significant estimates from genetically predicted gut microbiota {(A)class.Bacilli;(B)class.Bacteroidia;(C)family.BacteroidalesS24.7;(D)genus.Butyricimonas;(E)genus.Lachnospira;(F)order.Bacteroidales; (G) order.Lactobacillales} on Osteomyelitis



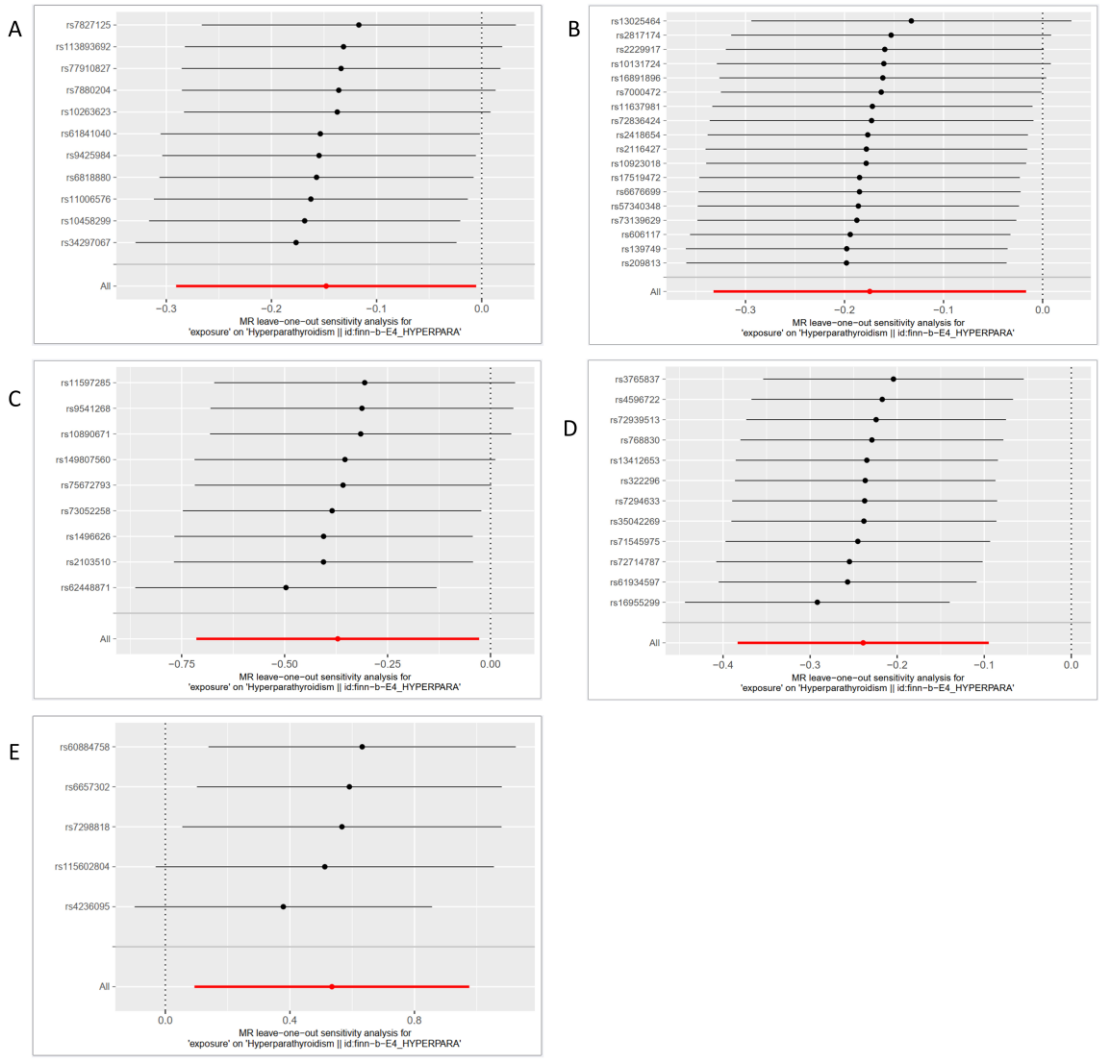
Supplement Figure S5

Leave-one-out plots of significant and nominal significant estimates from genetically predicted gut microbiota {(A) family.Bifidobacteriaceae;(B)family.Pasteurellaceae;(C)genus..Eubacteriumruminantium;(D)genus.Alistipes;(E)genus.Hungatella;(F)order.Bifidobacteriales;(G)order.Pasteurellales} on Hypoparathyroidism



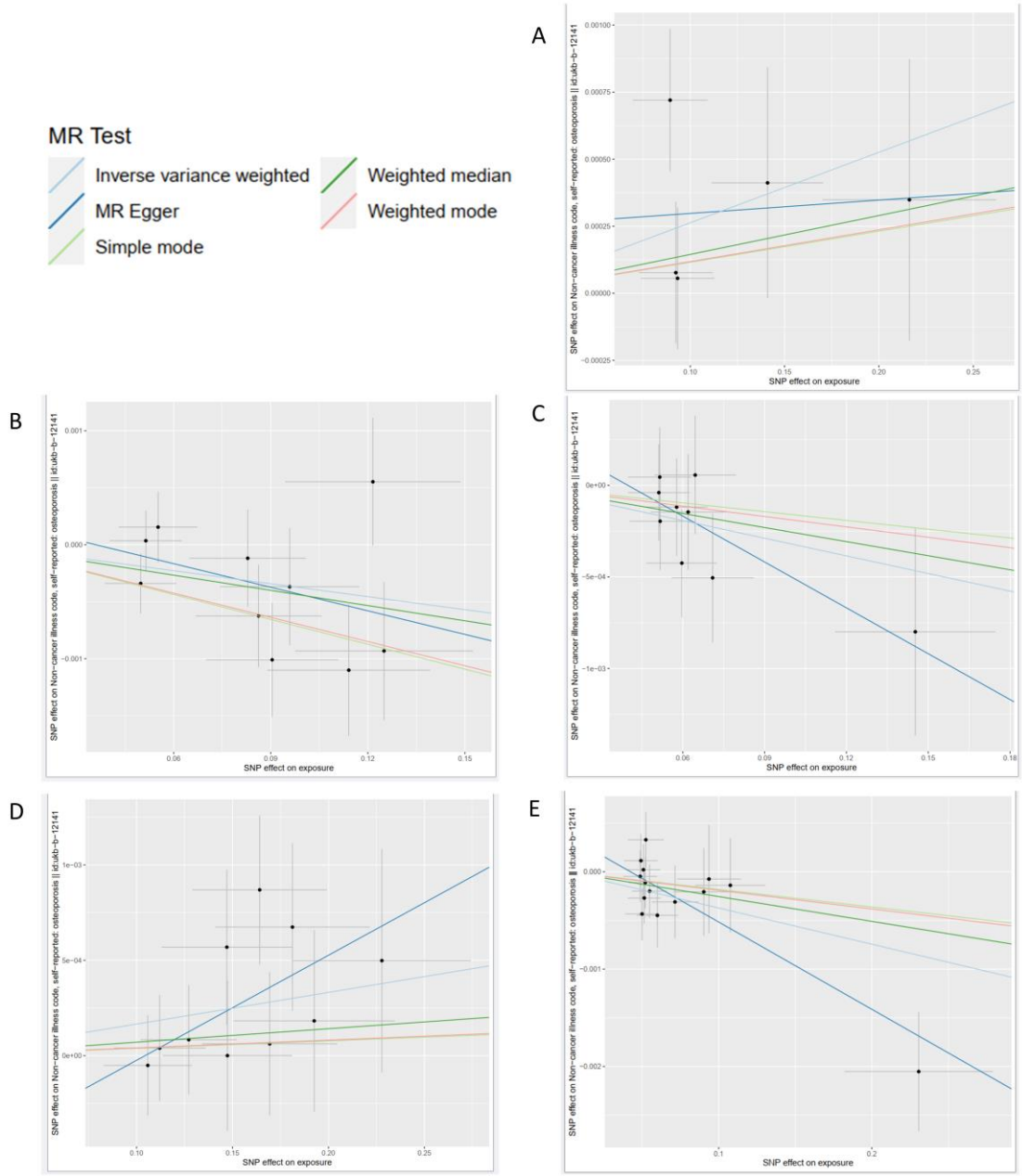
Supplement Figure S6

Leave-one-out plots of significant and nominal significant estimates from genetically predicted gut microbiota {(A)genus..Eubacteriumnodatum;(B)genus..Eubacteriumruminantium;(C)genus.Collinsella;(D)genus.Gordonibacter;(E)genus.Parabacteroides} on Hyperparathyroidism



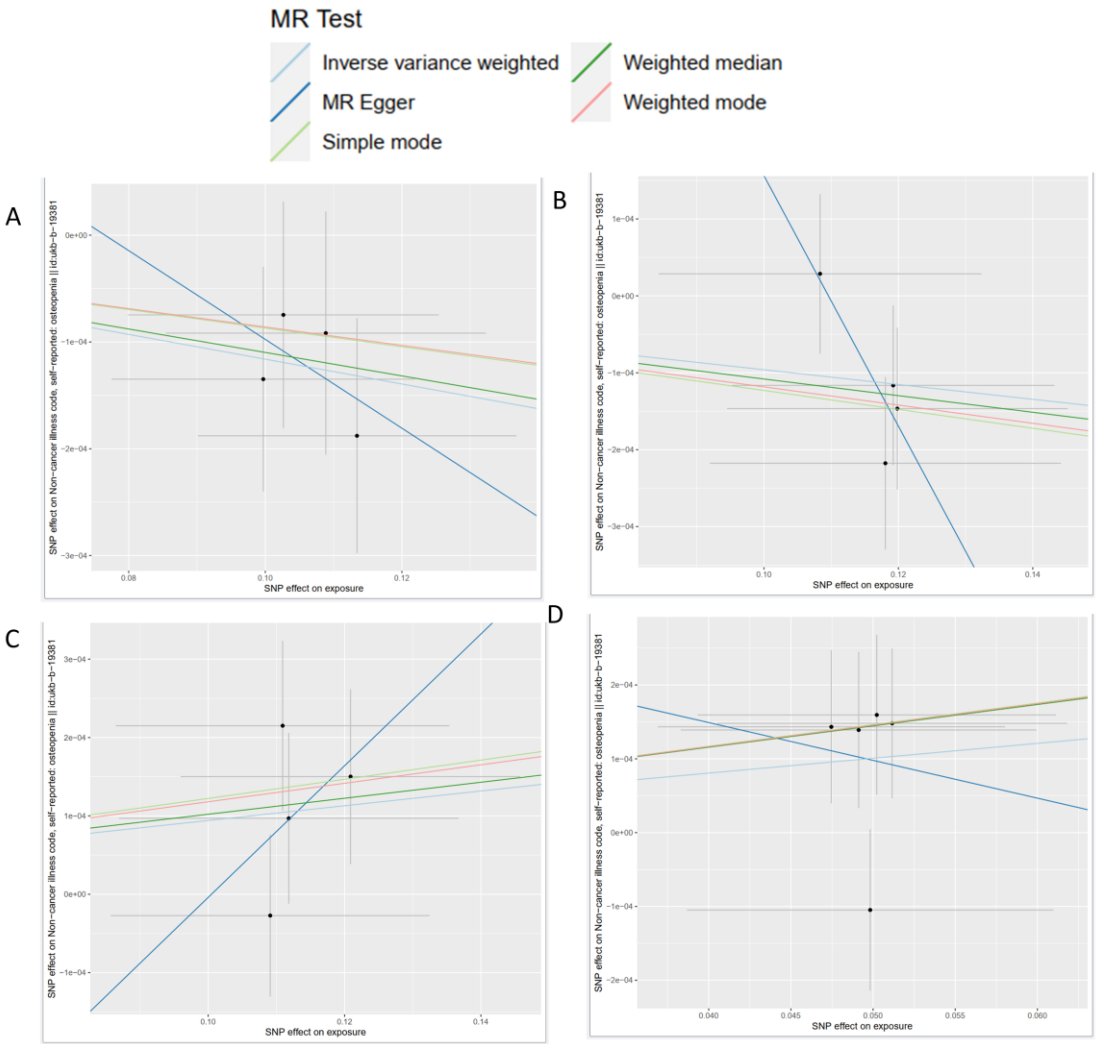
Supplement Figure S7

Scatter plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)genus..Eubacteriumoxidoreducens;(B)genus.ChristensenellaceaeR.7;(C)genus.Coprococcus3;(D)genus.Howardella; (E) genus.LachnospiraceaeNK4A136} on Osteoporosis



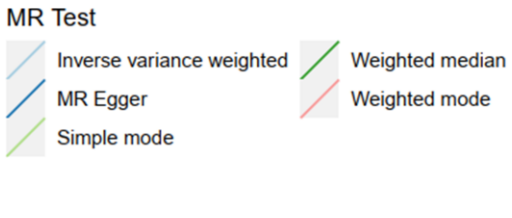
Supplement Figure S8

Scatter plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)genus..Clostridiuminnocuum;(B)genus.Butyrivibrio;(C)genus.RuminococcaceaeUCG011;(D)phylum.Proteobacteria}on Osteopenia



Supplement Figure S9

Scatter plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)class.Erysipelotrichia;(B)family.Erysipelotrichaceae;(C)family.Family XIII;(D)genus.ChristensenellaceaeR.7;(E)genus.Dorea;(F)genus.Parabacteroides;(G)order.Erysipelotrichales} on Osteonecrosis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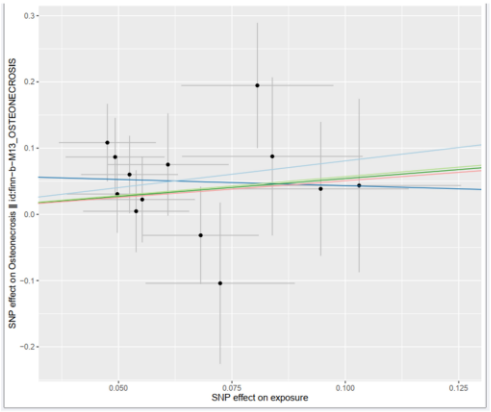
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode

A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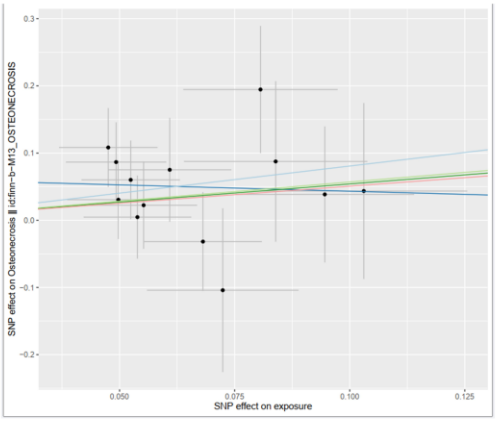
SNP effect on exposure

B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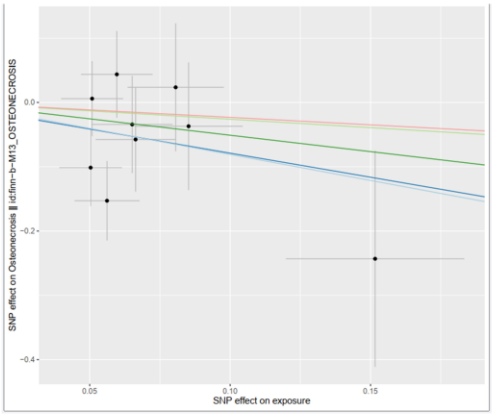
C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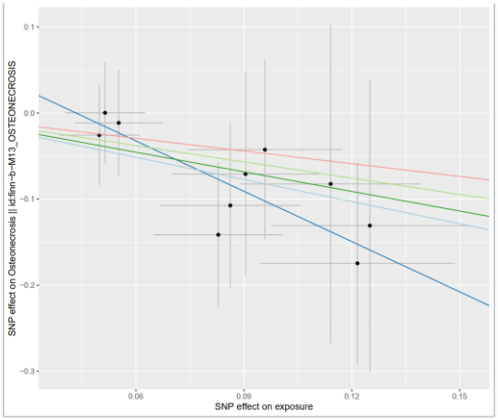
SNP effect on exposure

D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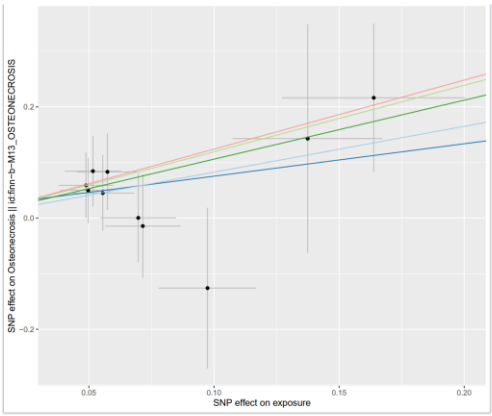
SNP effect on exposure

E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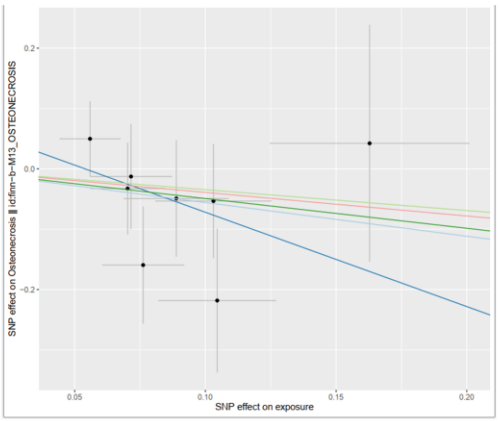
SNP effect on exposure

F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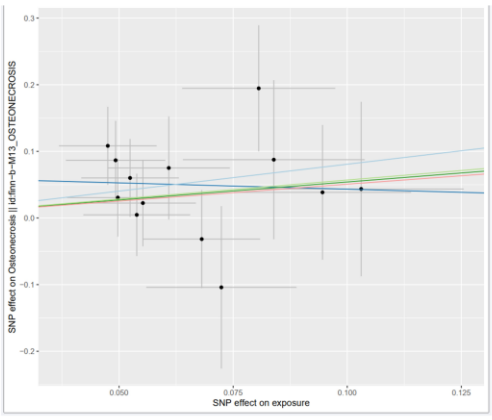
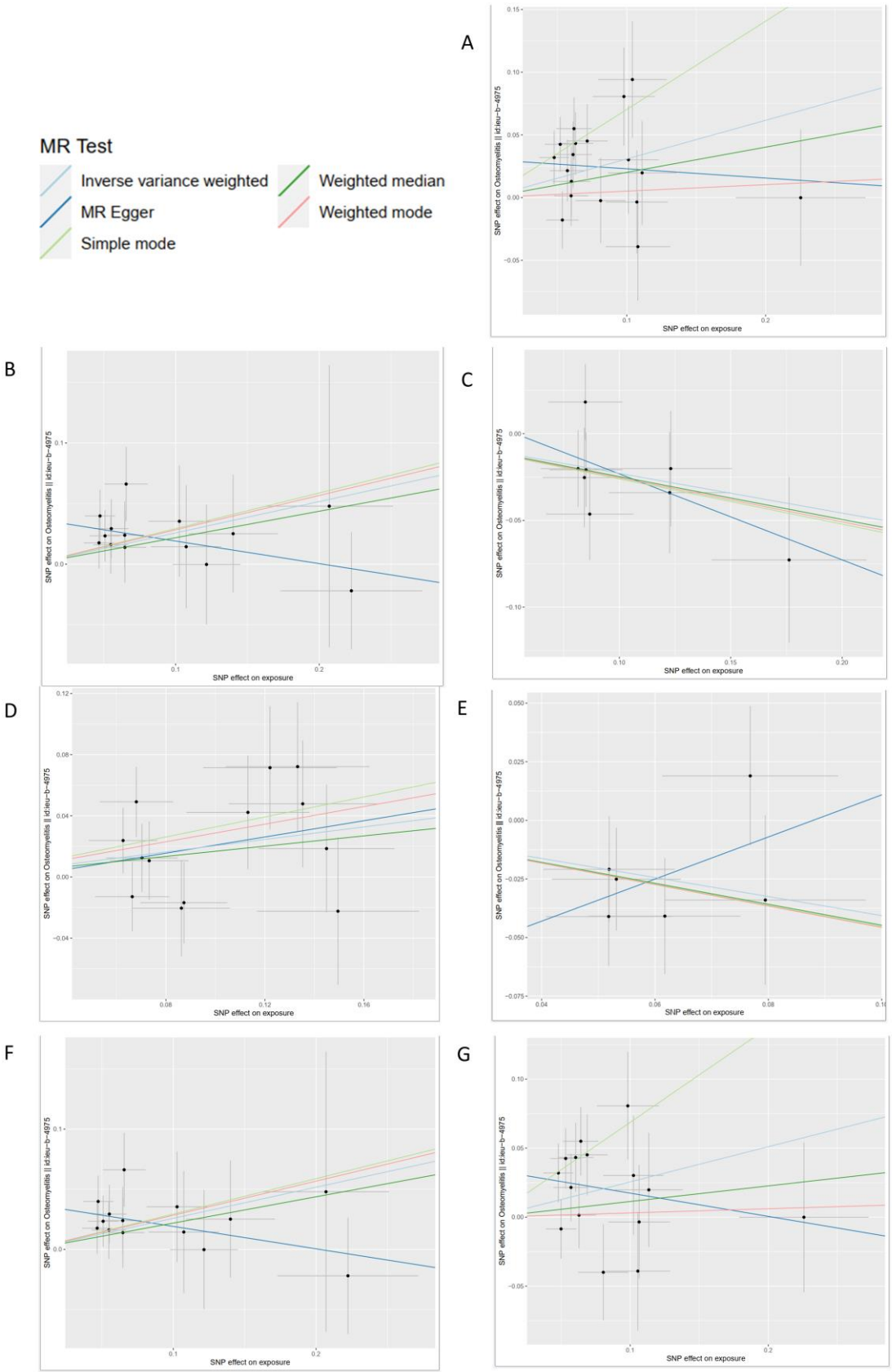
SNP effect on exposure

G


SNP effect on Osteonecrosis || id:finn-b-M13_OSTEONECROSIS
SNP effect on exposure

Supplement Figure S10

Scatter plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)class.Bacilli;(B)class.Bacteroidia;(C)family.BacteroidalesS24.7;(D)genus.Butyricimonas;(E)genus.Lachnospira;(F)order.Bacteroidales; (G) order.Lactobacillales} on Osteomyelitis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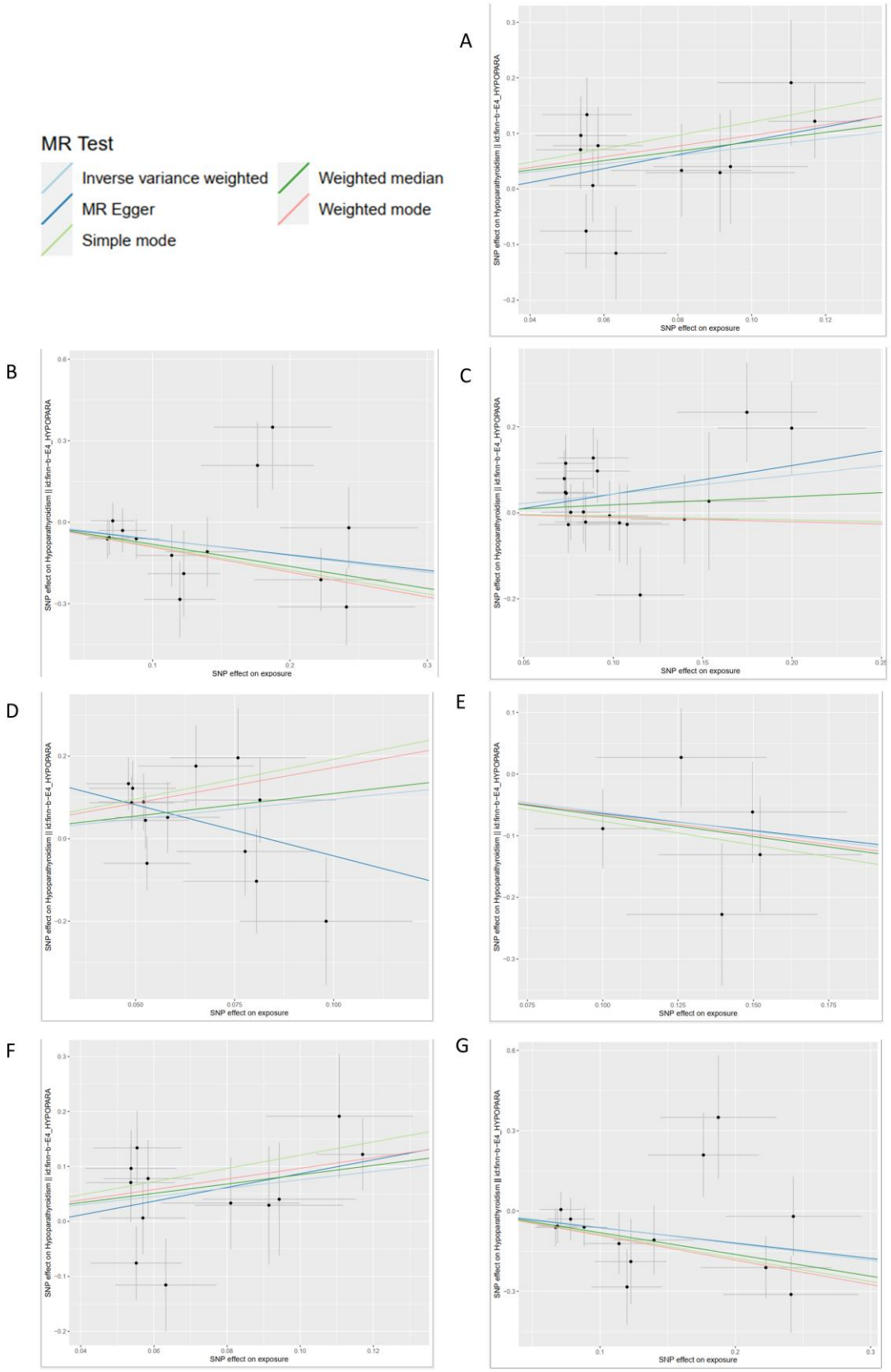
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
A
B
C
D
E
F
G
SNP effect on Osteomyelitis || id:ieu-b-4975
SNP effect on exposure

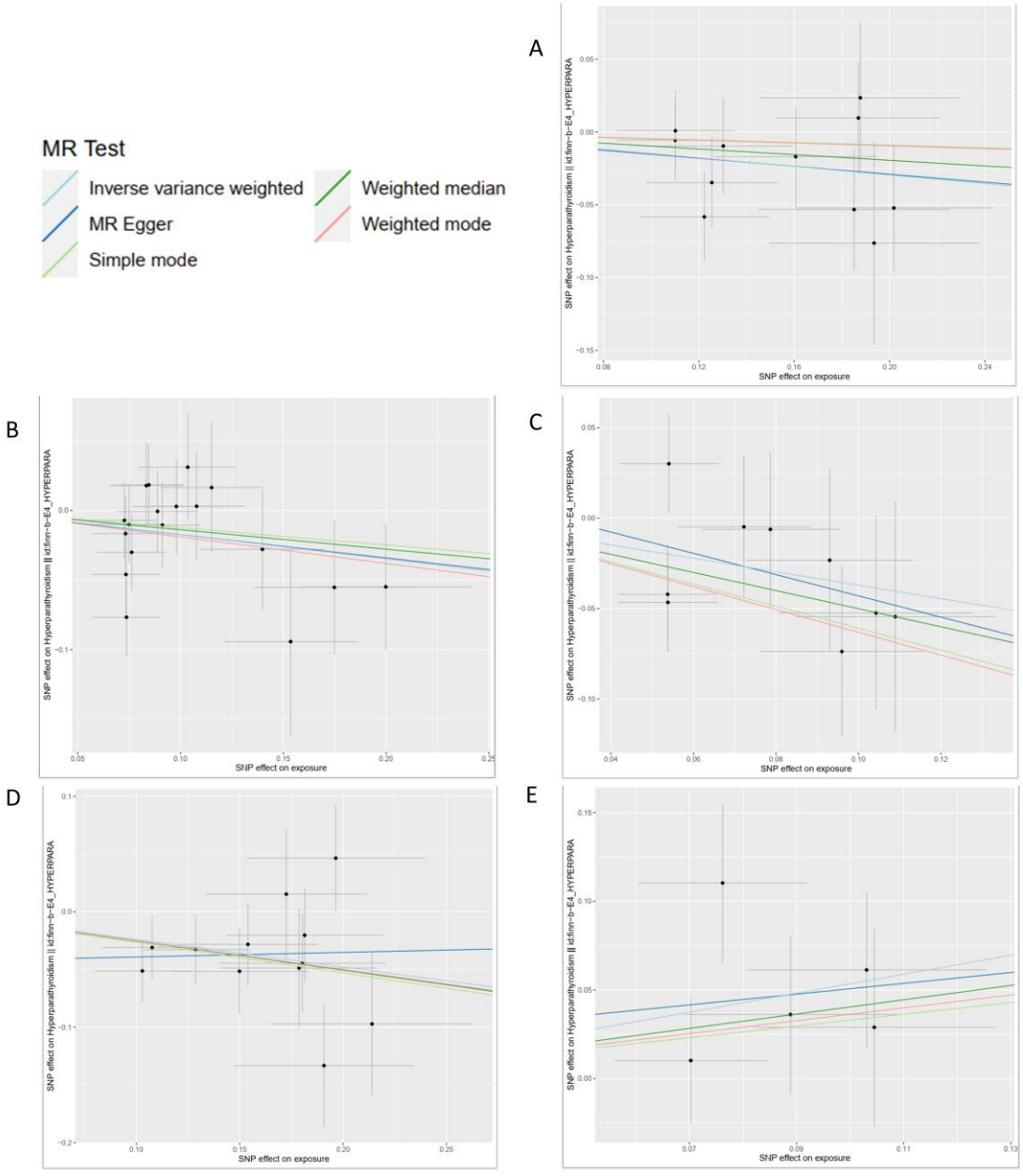
Supplement Figure S11

Scatter plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)family.Bifidobacteriaceae;(B)family.Pasteurellaceae;(C)genus..Eubacteriumruminantium;(D)genus.Alistipes;(E)genus.Hungatella;(F)order.Bifidobacteriales;(G)order.Pasteurellales}on Hypoparathyroidism


MR Test
Inverse variance weighted
MR Egger
Simple mode
Weighted median
Weighted mode
A
B
C
D
E
F
G
SNP effect on Hypoparathyroidism || id.finn-b-E4_HYPOPARA
SNP effect on exposure

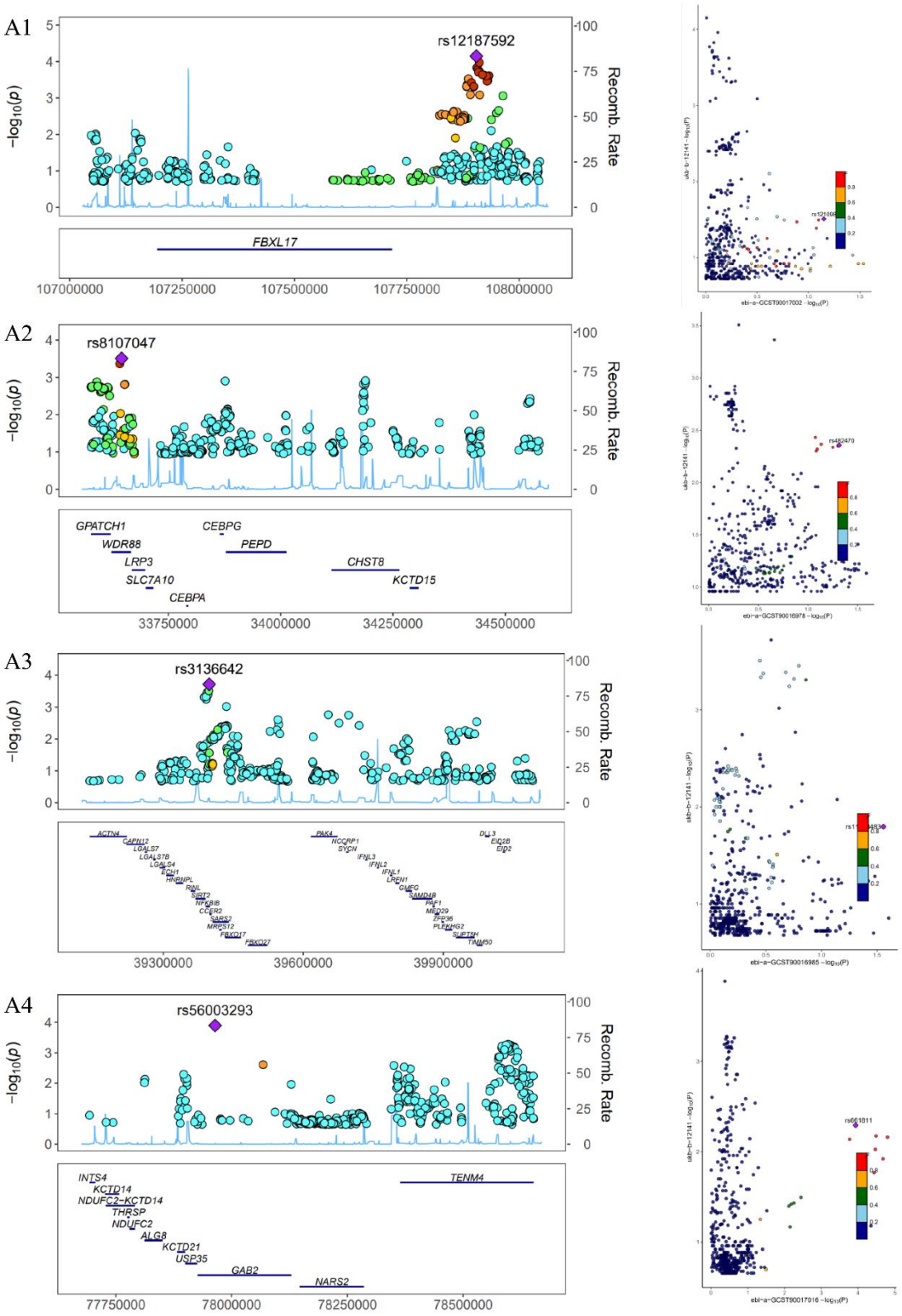
Supplement Figure S12

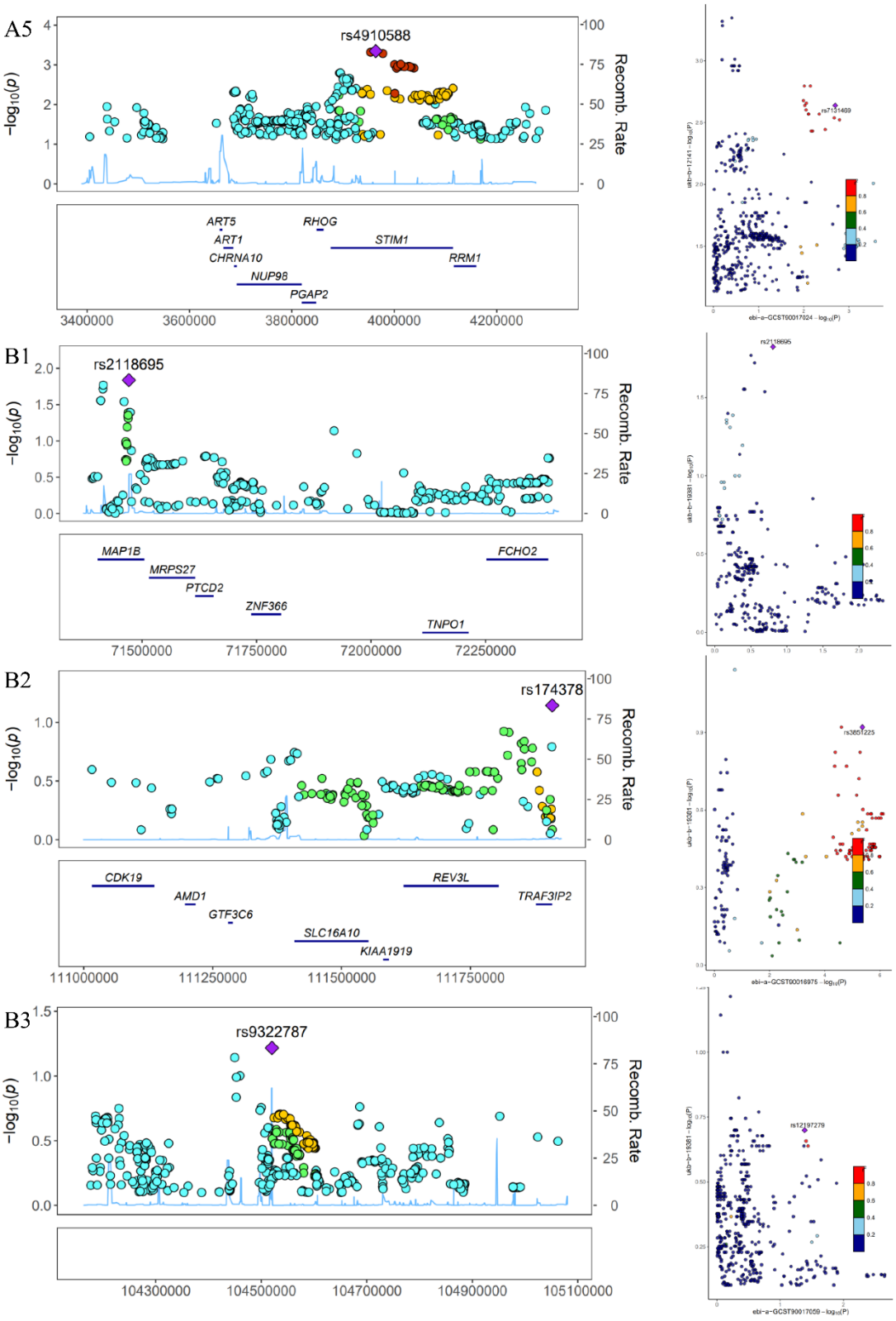
Scatter plots of significant and nominal significant estimates from genetically predicted gut microbiota{(A)genus..Eubacteriumnodatum;(B)genus..Eubacteriumruminantium;(C)genus.Collinsella;(D)genus.Gordonibacter;(E)genus.Parabacteroides} on Hyperparathyroidism



Supplement Figure S13

LocusZoom and LocusCompare plots of significant and nominal significant estimates from genetically predicted gut microbiota on six metabolic bone diseases.

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ART1
STIM1
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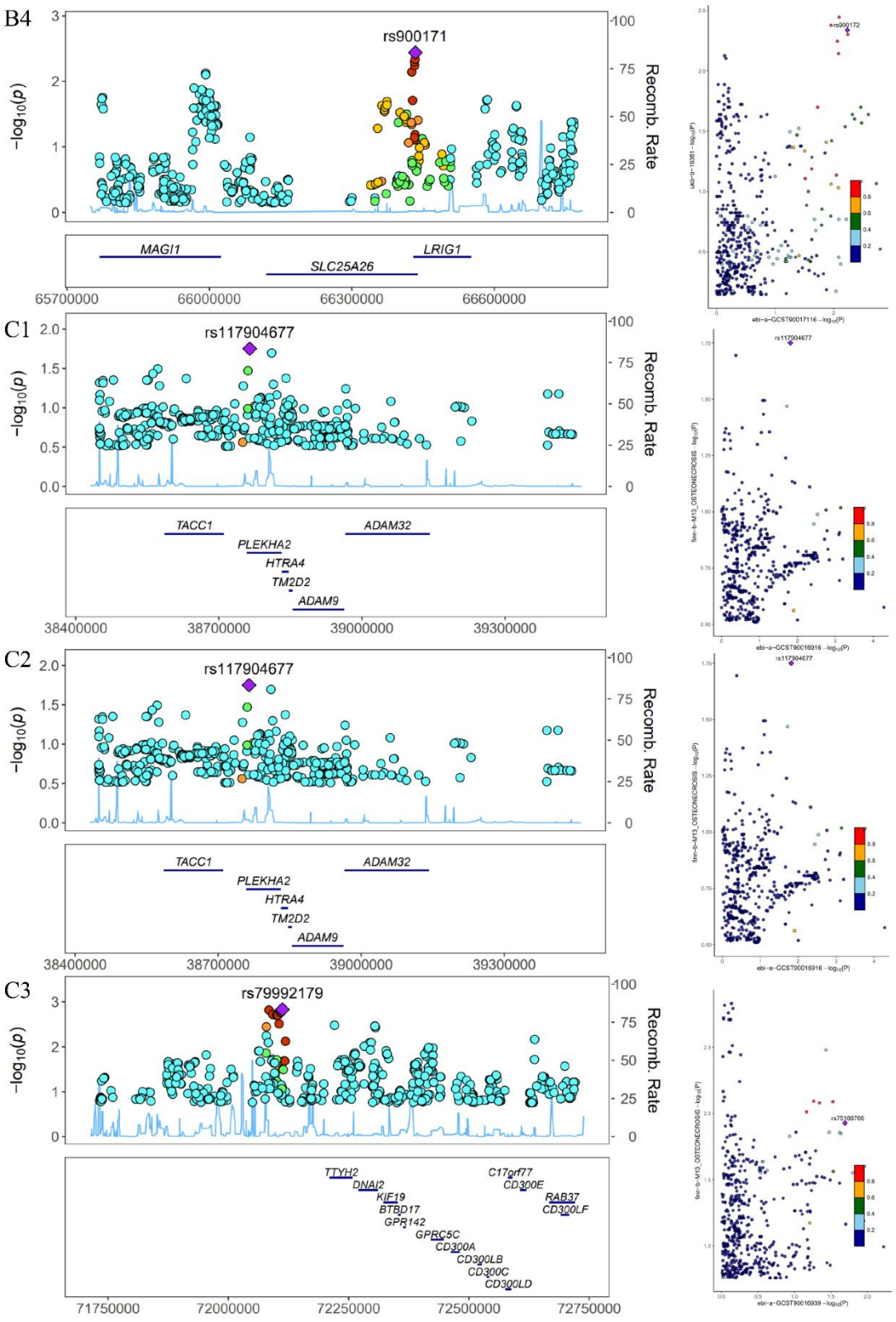
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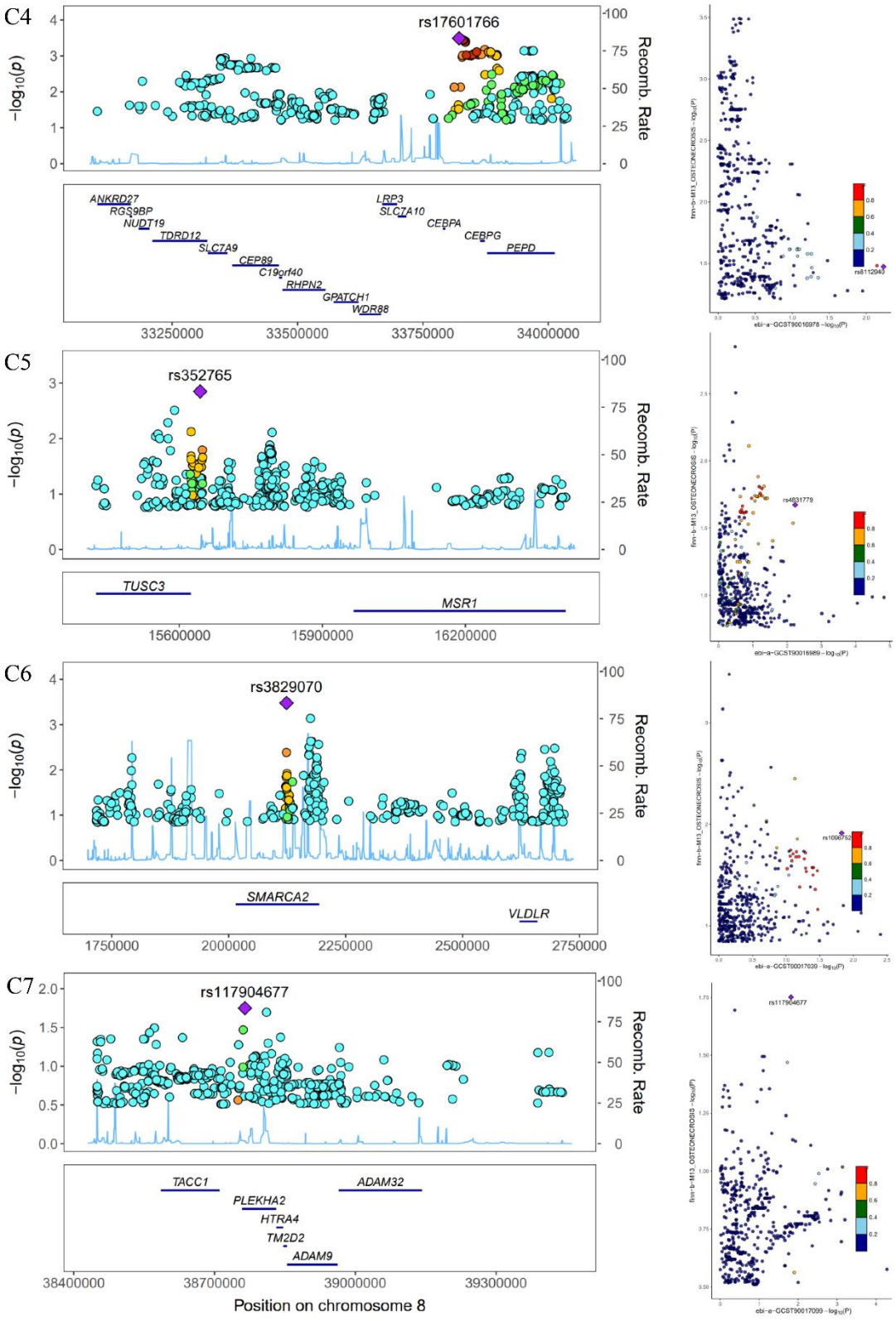
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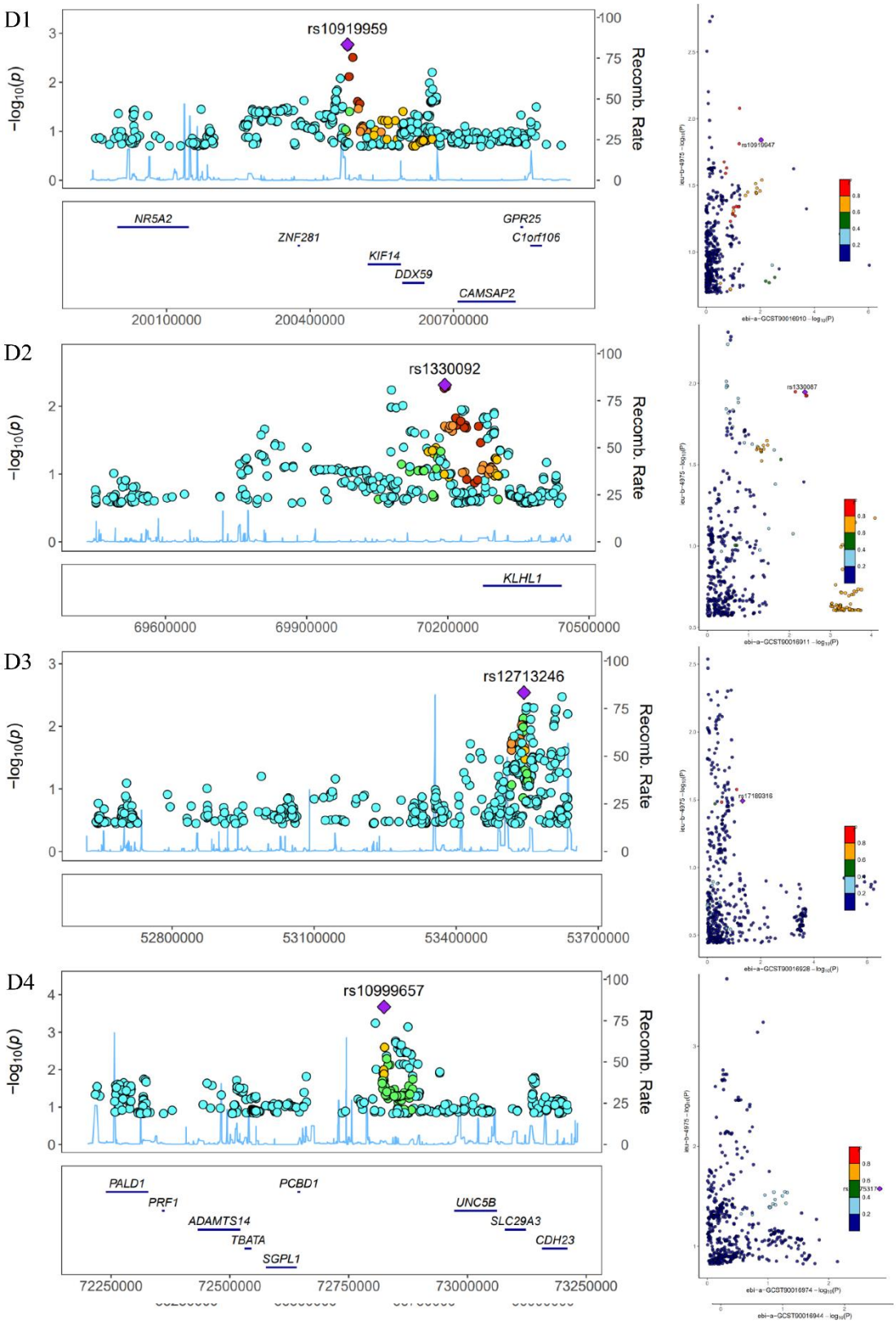
Position on chromosome 8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D3
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D4
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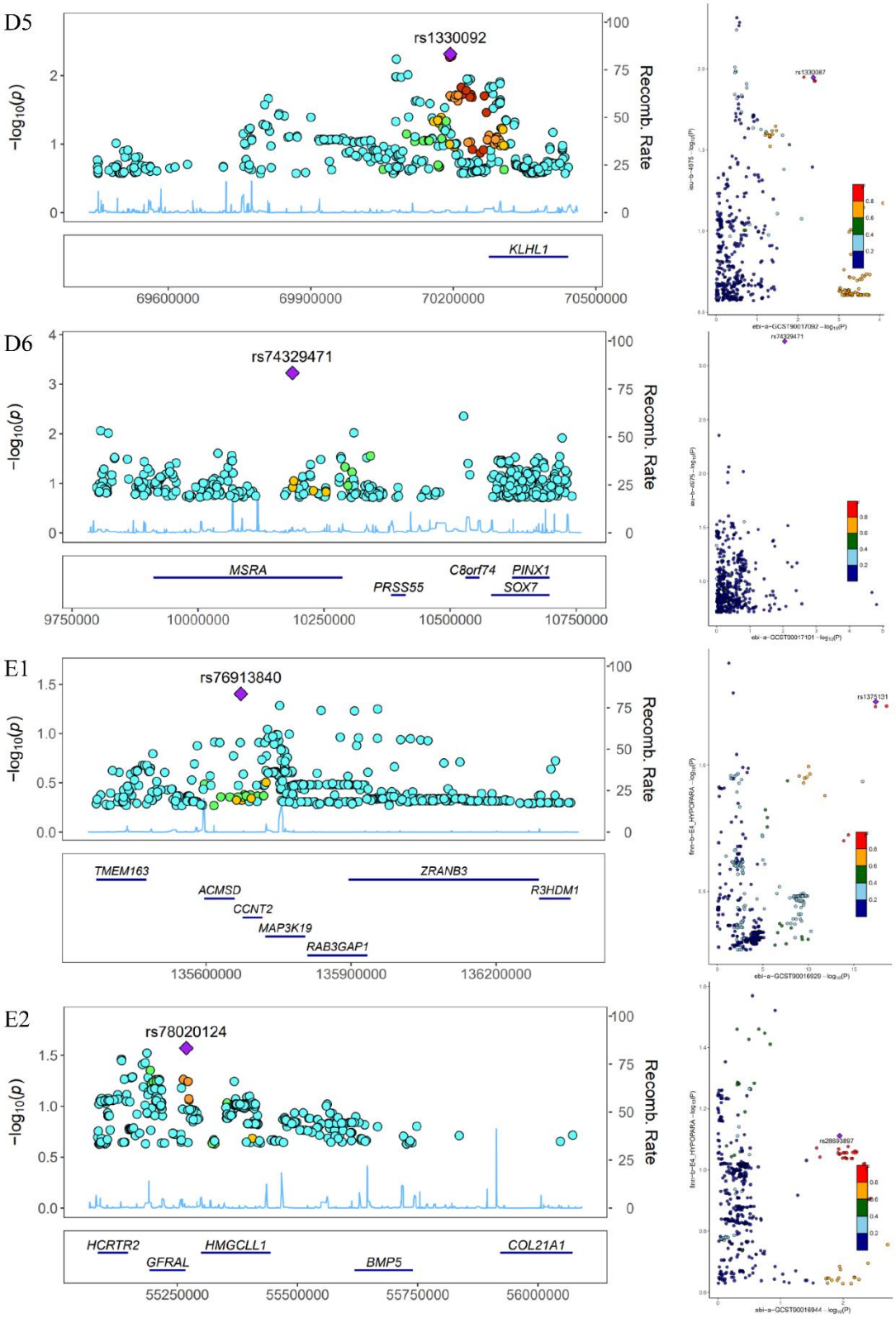
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ACMSD
R3HDM1
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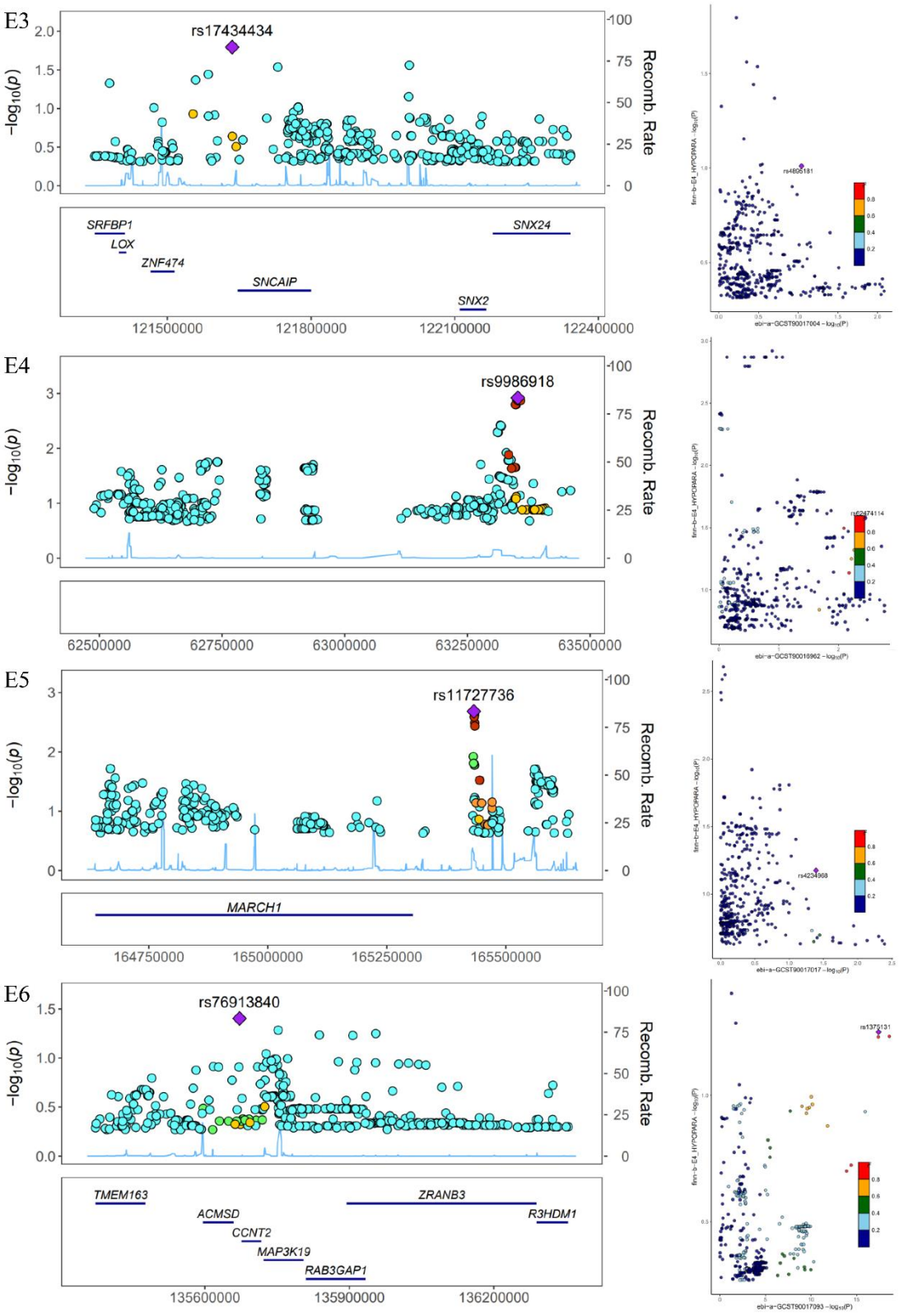
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LOX
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SNX2
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62500000
62750000
63000000
63250000
63500000
E5
rs11727736
MARCH1
164750000
165000000
165250000
165500000
E6
rs76913840
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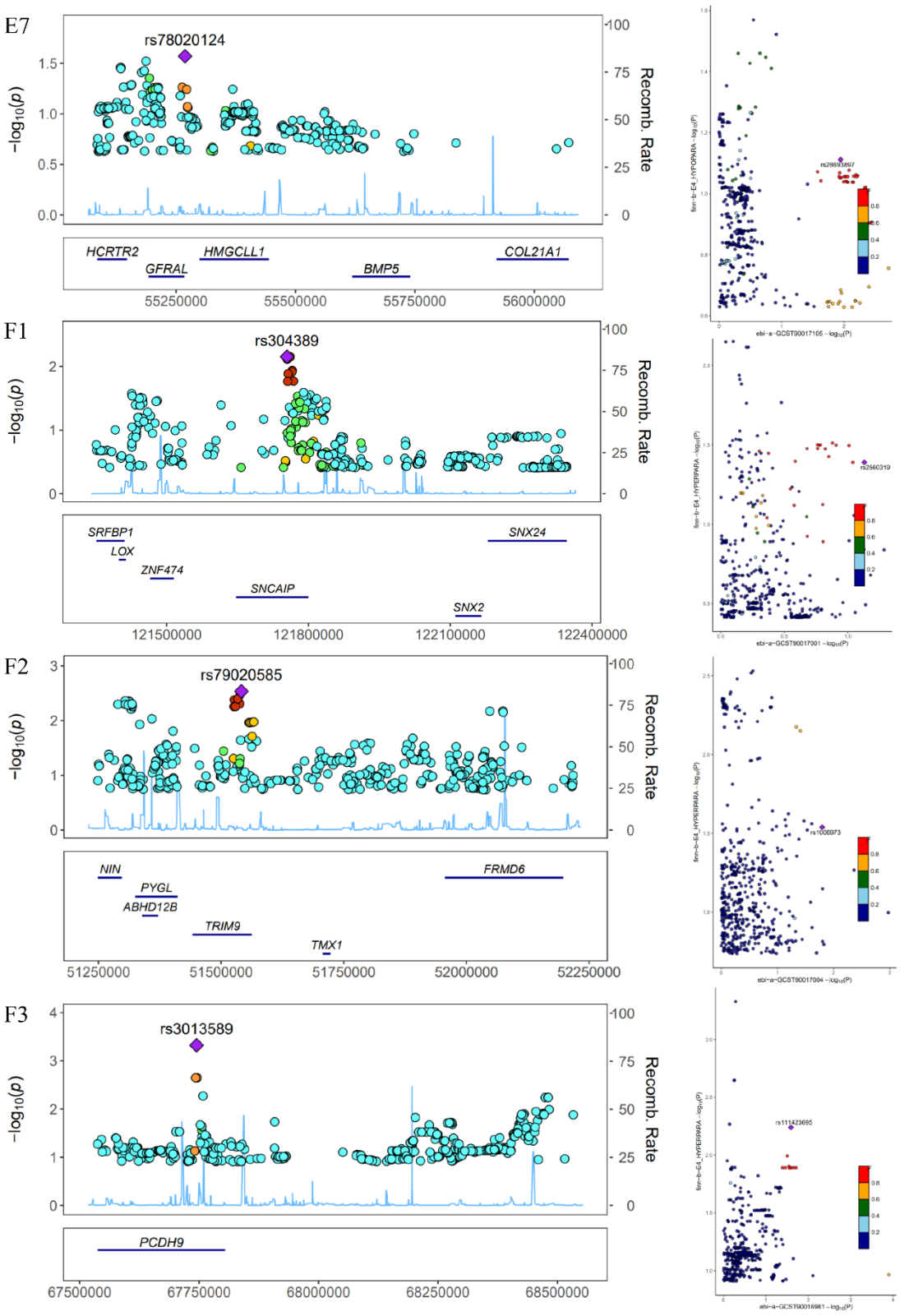
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Recomb. Rate
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GFRAL
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COL21A1
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56000000
F1
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SRFBP1
LOX
ZNF474
SNCAIP
SNX2
SNX24
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F2
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NIN
PYGL
ABHD12B
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TMX1
FRMD6
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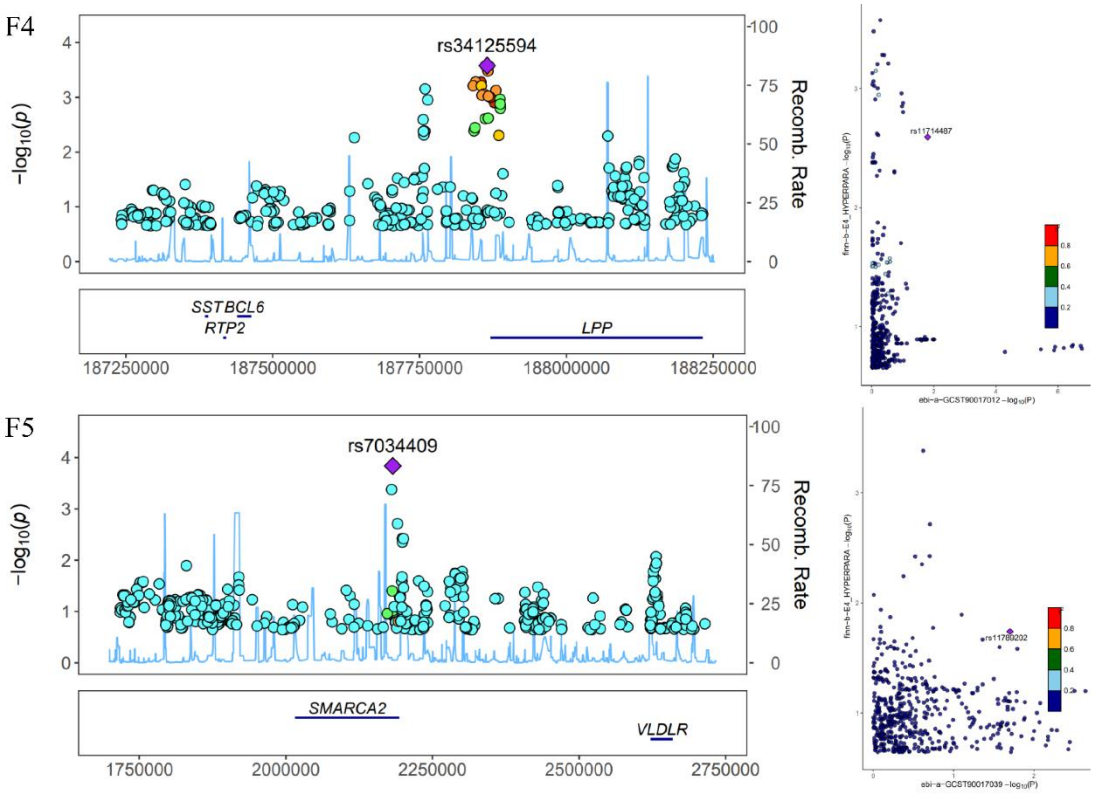

For each colocalized locus (PP.H4 < 0.75) identified for corresponding trait pair, the left panel depicts the PLACO results using LocusZoom plot, and the right panel compares two single-trait GWAS statistics of corresponding trait pair for each variant using LocusCompare plot. For the LocusZoom plot, the x-axis shows the genomic position for each variant, and the y-axis shows -log10 *P* values from PLCAO results. The top variant with the smallest P_{PLACO} in each locus is indicated in purple diamond. The color of each variant represents its LD relationship with the top variant. For the LocusCompare plot, each dot represents a variant, the x-axis shows the -log10 P_{GWAS} from corresponding GWAS of metabolic bone diseases, and the y-axis shows -log10 P_{GWAS} from corresponding GWAS gut microbiota. The candidate shared causal variant identified by pairwise colocalization analysis is also indicated in purple diamond. The color of each variant represents its LD relationship with the candidate shared causal variant. All genomic location is based on reference genome hg19, and LD calculation is based on 1000 Genomes Project of European population. {(A1)genus..Eubacteriumoxidoreducens;(A2)genus.ChristensenellaceaeR.7;(A3)genus.Coprococcus3;(A4)genus.Howardella; (A5) genus.LachnospiraceaeNK4A136} for osteoporosis.
{(B1)genus..Clostridiuminnocuum;(B2)genus.Butyrivibrio;(B3)genus.RuminococcaceaeUCG011;(B4)phylum.Proteobacteria} for Osteopenia.
{(C1)class.Erysipelotrichia;(C2family.Erysipelotrichaceae;(C3)family.FamilyXIII;(C4)genus.ChristensenellaceaeR.7;(C5)genus.Dorea;(C6)genus.Parabacteroides;(C7)order.Erysipelotrichales} for Osteonecrosis.
{(D11)class.Bacilli;(D2)class.Bacteroidia;(D3)family.BacteroidalesS24.7;(D4)genus.Butyricimonas;(NA)genus.Lachnospira;(D5)order.Bacteroidales; (D6)

order.Lactobacillales} for Osteomyelitis.
{(E1)family.Bifidobacteriaceae;(E2)family.Pasteurellaceae;(E3)genus..Eubacteriumruminantium;(E4)genus.Alistipes;(E5)genus.Hungatella;(E6)order.Bifidobacteriales;(E7)order.Pasteurellales} for Hypoparathyroidism.
{(F1)genus..Eubacteriumnodatum;(F2)genus..Eubacteriumruminantium;(F3)genus.Collinsella;(F4)genus.Gordonibacter;(F5)genus.Parabacteroides} for Hyperparathyroidism