

GWAS analysis and digital pathology at patients without MASLD improvement: a prospective cohort 1-year study



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Background and Aim

Lifestyle intervention is the primary approach for managing MASLD. Identifying genetic traits in non-responders may pave the way for personalized pharmacotherapy in this population.

Method

All participants completed questionnaires, blood tests, MRI-PDFF assessments and health education. Genetic sequencing by GWAS chip and bootstrap analysis was performed (N=325). SHG/TPEF microscopy with computer-assisted analysis was used for 146 pathological specimens. MASLD was diagnosed based on new criteria, and disease regression was assessed by comparing MRI-PDFF findings (Liver Fat Content reduction $\geq 30\%$).

Results

In this 12-month study, 145 (99%) and 602 (83%) participants were diagnosed with MASLD via liver biopsy and MRI-PDFF, respectively.

Genetic analysis in the whole cohort (N=125 vs. 200) revealed significant effects of VPS8(rs1011147, T>C) and DPP6(rs144355748, G>A) mutations on disease progression (MRI-PDFF changes for wild-type vs. mutant: -9.2% vs. 0.3% and -6.5% vs. 0.7%, respectively). After adjusting for lifestyle factors (smoking, alcohol, physical activity, sedentariness), mediation analysis showed that GRS significantly influences MASLD remission (effect = 0.154). The indirect effect through weight reduction is 0.053 (total effect = 0.208, all P<0.05). Functional enrichment analysis revealed a focus on the RISC complex, RNAi effector complex, and Estrogen signaling pathway for these genes.

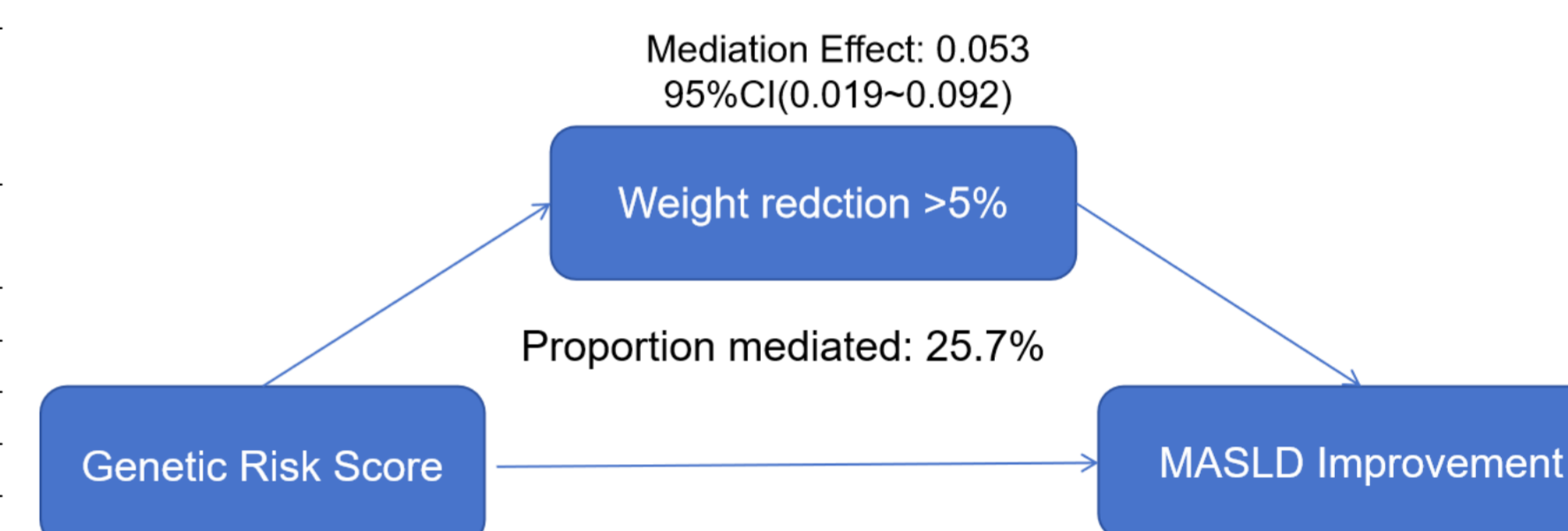
In the 5% weight loss group (N=200), 28 SNPs affecting MASLD regression were identified, and GRS scores calculated. Low GRS individuals displayed more improvement in fibrosis (dStrLength: -3.6 vs. 191.5; dSHG: -0.2 vs. 2.8) and fat change (dArea: -24.5 vs. 5.6; dABubble: -168.2 vs. 58.6; dAreaCV: -14.1 vs. 14.4) compared to high GRS individuals. MASLD patients achieving over 5% weight loss (N=200) supported by digital pathology showing significant decreases in most steatosis markers (Area: -9.7; Area PT: -6.6; ABubblePT: -55.7) and some fibrosis-related markers (Str: -7.7, StrLenthPS: -7093), indicating notable improvements in fat content and select fibrosis-related measures. However, of those who lost 5% weight, 52 individuals (26%) didn't achieve remission.

Baseline and Relative Change of Indicators, Stratified by Disease Improvement Status

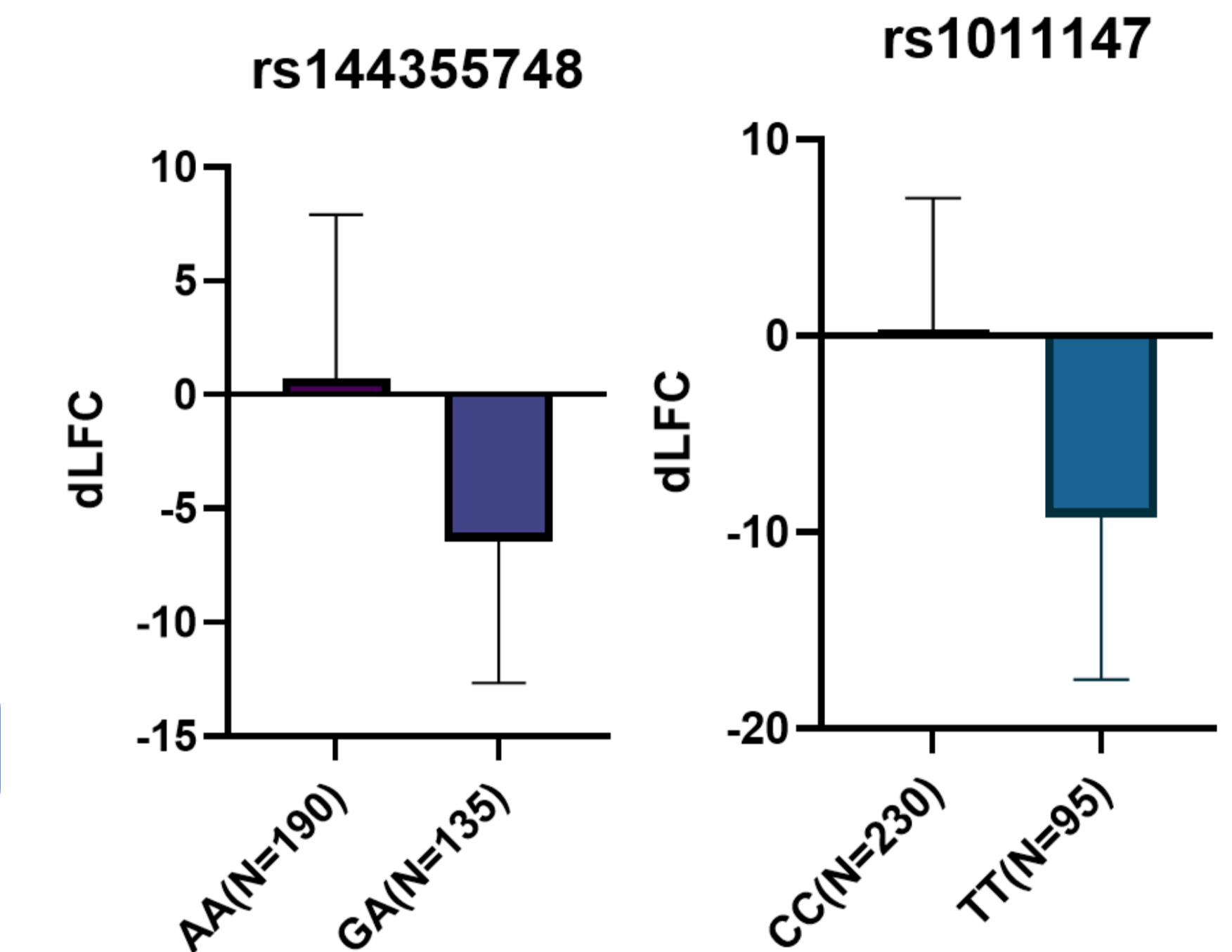
Variables	Improve (n = 213)	Keep (n = 330)	Progress (n = 181)	p-value
Baseline Characteristics				
Age, year	40 (16)	40 (15)	41 (17)	0.191
Male, N(%)	109 (71%)	273 (70%)	113 (62%)	0.1343
Weight, kg	79 (14.9)	79.1 (17.05)	77 (15.1)	0.0598
BMI, kg/m ²	28.1 (3.8)	28.1 (4.47)	27.5 (5.2)	0.1639
LFC, %*	13.8 (11.67)	11.81 (10.04)	7.12 (6.18)	< 0.0001
Steatotic degree -Health, N(%)*	16 (10%)	45 (12%)	61 (34%)	< 0.0001
- Mild steatosis, N(%)	63 (41%)	196 (50%)	100 (55%)	
- Moderate steatosis, N(%)	65 (42%)	126 (32%)	20 (11%)	
- Severe steatosis, N(%)	9 (6%)	23 (6%)	0 (0%)	
Changes from Baseline				
dWeight, kg*	-2.64 (6.51)	0.6 (4.27)	2.14 (4.29)	< 0.0001
dBMI, kg/m ² *	-0.8 (1.8)	0.3 (1.2)	0.5 (1.2)	< 0.0001
dAC, cm*	-4 (6.8)	-1.9 (6.5)	-0.7 (6.9)	< 0.0001
dWC, cm*	-1.5 (7.4)	-0.4 (8)	0.4 (7.8)	0.0157
dHC, cm*	-2 (7)	-0.5 (6.6)	-0.2 (6.4)	0.0113
dSBP, mmHg*	-4 (17)	1 (18)	1 (15)	< 0.0001
dBPP, mmHg*	-3 (14)	-2 (13)	1 (10)	0.0007
dCAP, db/m*	-32 (53)	1.5 (44.25)	24 (56.25)	< 0.0001
dLSM, kpa*	-0.7 (1.85)	-0.1 (2)	0.3 (1.9)	< 0.0001
dLFC, %*	-45.67 (18.83)	-3.48 (26.35)	62.66 (53.85)	< 0.0001
dAST, U/L*	-7.2 (14.9)	-1.6 (12.95)	3 (11.1)	< 0.0001
dALT, U/L*	-16.2 (35.8)	-4 (0)	3.5 (23.3)	< 0.0001
dGGT, U/L*	-12 (22.6)	-1.15 (15.7)	5.5 (18.9)	< 0.0001
dTC, mmol/L*	-0.19 (1.08)	0.05 (0.9)	0.19 (0.98)	< 0.0001
dTG, mmol/L*	-0.51 (1.22)	-0.15 (1.2)	0.29 (1.35)	< 0.0001
dHDL, mmol/L	0 (0.24)	0.02 (0.23)	0.02 (0.25)	0.6511
dLDL, mmol/L*	-0.12 (0.87)	0.05 (0.76)	0.17 (0.83)	0.0019
dGlucose, mmol/L*	-0.21 (0.87)	-0.04 (0.88)	-0.08 (1.01)	0.0135
dInsulin, pmol/L*	-7.9 (75.9)	6.82 (71.36)	17.3 (59.32)	0.0009
dHOMA-IR*	-0.35 (3.27)	0.34 (2.94)	0.54 (2.71)	0.0001

Mediation analysis reveals the impact of genes and weight loss on disease progression.

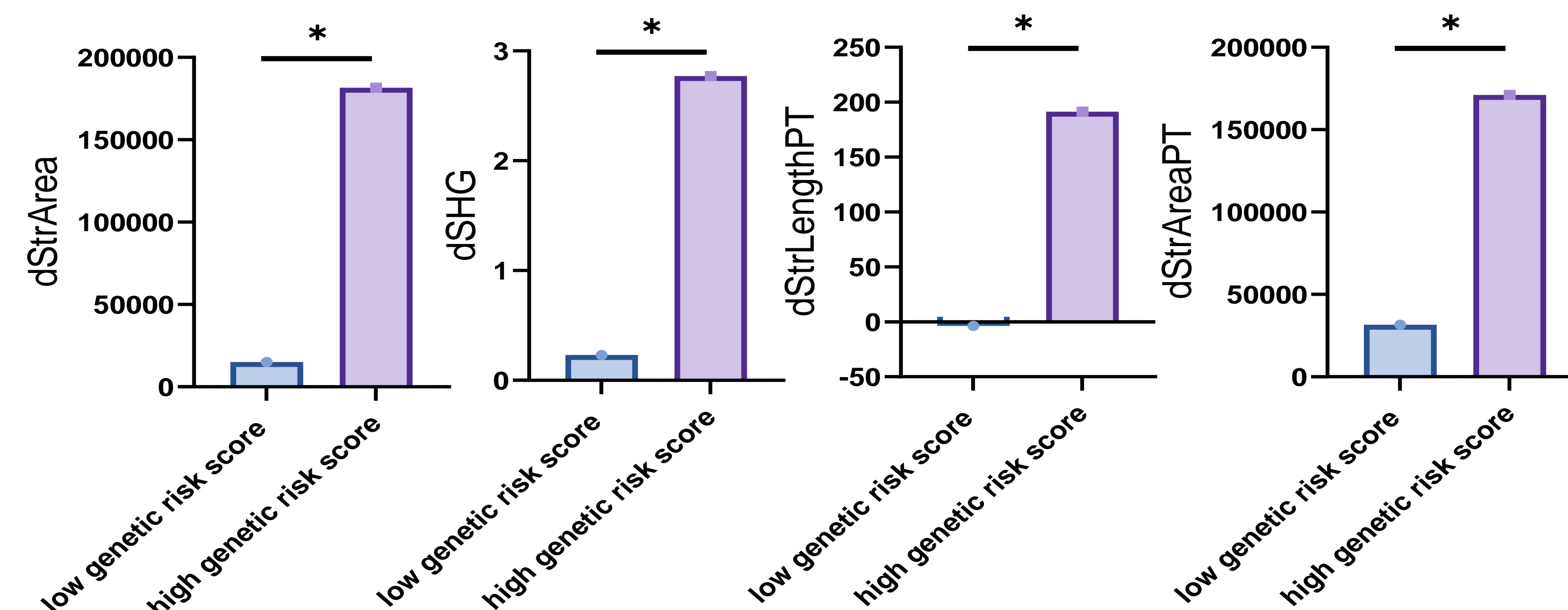
Effect	Estimate	95% CI	P
Indirect	0.053	0.019~0.092	0.002
Direct	0.154	0.089~0.219	< 0.001
Total	0.208	0.132~0.275	< 0.001
Proportion Mediated	0.257	0.094~0.442	0.002



Disease progression-associated variant VPS8(rs1011147, T>C) and DPP6(rs144355748, G>A) shows a trend towards better remission with homozygous wild-type status



Comparison of digital pathology changes (Fibrosis markers) over one year in 5% weight loss group stratified by GRS score. High genetic risk score (N=9), Low genetic risk score (N=11)



Conclusions

Our study underscores the role of genetic traits in determining disease progression in MASLD patients, genetic traits play an important role in MASLD progression, pointing towards personalized medicine possibilities.

