Supplementary

Supplementary Table S1. List of 88 selected genes in the peroxisome pathway

Dataset	Name of pathway	Number of genes
GO	GO_PEROXISOME_ORGANIZATION	33
GO	GO_PROTEIN_IMPORT_INTO_PEROXISOME_MATRIX	13
KEGG	KEGG_PEROXISOME	78
REACTOME	-	0
BIOCARTA	-	0
PID	-	0
Total	*ABCD3, ACBD5, ACOT8, ACOX1, DNM1L, FIS1, LONP2, MFF, PEX1, PEX10, PEX11A, PEX11B, PEX11G, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX5L, PEX6, PEX7, PIK3R4, RAB8B, SCP2, SEC16B, TMEM135, TRAPPC8, ZFAND6, ABCD2, ABCD4, ACAA1, ACOX2, ACOX3, ACSL1, ACSL3, ACSL5, ACSL6, AGPS, AGXT, AMACR, BAAT, CAT, CRAT, CROT, DAO, DDO, DECR2, DHRS4, ECH1, ECI2, EHHADH, EPHX2, FAR1, FAR2, GNPAT, GSTK1, HACL1, HAO1, HAO2, HMGCL, HSD17B4, IDH1, IDH2, MLYCD, MPV17, MPV17L, MVK, NOS2, NUDT12, NUDT19, PAOX, PECR, PHYH, PIPOX, PMVK, PRDX1, PRDX5, PXMP2, PXMP4, SLC25A17, SLC27A2, SOD1, SOD2, XDH* (after removing the duplicated 34 genes, deleting *ABCD1* and *ACSL4* in X chromosome)	88

Keyword: peroxisome; Organism: Homo sapiens; Website: http://software.broadinstitute.org/gsea/msigdb/search.jsp

Supplementary Table S2. Multiple testing corrections of the two independent SNPs in MDACC study

SNP	Location	Gene	Type	P[a]	FDR 0.1	BFDP (Prior probability[b])		
						0.01	0.001	
rs567403	11q14.2	*TMEM135*	Imputed	0.036	0.947	0.782	0.975	0.998
rs7969508	12p13.31	*PEX5*	Genotyped	0.029	0.947	0.780	0.975	0.997

[a]Multivariate analysis with adjustment for age, sex, Breslow thickness, tumor stage, ulceration and mitotic rate in an additive genetic model in the MDACC study; [b]Calculated using study subjects to detect an upper bound of 3.0 and a prior probability of 0.1. Abbreviations: BFDP, Bayesian false-discovery probability; FDR, false discovery rate; MDACC, The University of Texas MD Anderson Cancer Center; *PEX5*, Peroxisomal Biogenesis Factor 5; SNP, single-nucleotide polymorphism; *TMEM135*, transmembrane protein 135.

Supplementary Table S3. Stratified analysis of the risk genotypes of selected SNPs in the MDACC and NHS/HPFS datasets

Characteristics	0-1 NRG[a]		2 NRG[a]		Univariate analysis		Multivariate analysis[b]		Interaction[c]
	All	Death (%)	All	Death (%)	HR (95% CI)	P	HR (95% CI)	P	
MDACC									
Age (years)									
≤50	330	24 (7.27)	41	7 (17.07)	2.60 (1.12-6.03)	0.026	3.40 (1.41-8.22)	0.007	
>50	440	56 (12.73)	47	8 (17.02)	1.40 (0.67-2.93)	0.375	1.86 (0.87-3.94)	0.107	0.114
Sex									
Male	449	57 (12.69)	47	12 (25.53)	2.25 (1.21-4.19)	0.011	2.65 (1.41-4.98)	0.003	
Female	321	23 (7.17)	41	3 (7.32)	0.99 (0.30-3.31)	0.987	1.69 (0.49-5.90)	0.408	0.535
Stage									
I/II	637	44 (6.91)	72	7 (9.72)	1.42 (0.64-3.16)	0.387	2.29 (0.99-5.30)	0.053	
III/IV	133	36 (27.07)	16	8 (50.00)	2.37 (1.10-5.11)	0.028	2.63 (1.19-5.79)	0.017	0.740
Breslow thickness (mm)									
≤1	312	7 (2.24)	35	0 (0.00)	-	-	-	-	
>1	458	73 (15.94)	53	15 (28.30)	1.98 (1.13-3.45)	0.016	2.54 (1.44-4.48)	0.001	0.175
Ulceration									
No	609	42 (6.90)	72	6 (8.33)	1.20 (0.51-2.83)	0.673	1.49 (0.63-3.55)	0.368	
Yes	142	34 (23.94)	13	9 (69.23)	5.23 (2.45-11.04)	<0.0001	4.23 (1.89-9.47)	0.0004	0.086
Missing	22								
Mitotic rate (mm^2)									
≤1	249	7 (2.81)	26	2 (7.69)	2.70 (0.56-12.99)	0.216	6.84 (0.89-52.91)	0.065	
>1	521	73 (14.01)	62	13 (20.97)	1.63 (0.91-2.95)	0.104	2.24 (1.23-4.08)	0.009	0.423
NHS/HPFS									
Age (years)									
≤ 50	71	3 (4.23)	1	0 (0.00)	-	-	-	-	
> 50	317	39 (12.30)	20	6 (30.00)	2.82 (1.20-6.67)	0.018	2.83 (1.20-6.70)	0.018	0.347
Sex									
Male	132	16 (12.12)	6	1 (16.67)	1.96 (0.26-14.86)	0.516	1.69 (0.22-13.11)	0.614	
Female	256	26 (10.16)	15	5 (33.33)	3.76 (1.44-9.80)	0.007	3.24 (1.23-8.51)	0.017	0.484

[a] Risk genotypes included *TMEM135* rs567403 CG+GG, *PEX5* rs7969508 AG+GG; [b] Adjusted for age, sex, Breslow thickness, stage, ulceration and mitotic rate in Cox models of SNPs and CMSS in the MDACC dataset and adjusted for age and sex only in the NHS/HPFS dataset; [c] Interaction: the interaction between the risk genotypes and each clinical variable. Abbreviations: SNP, single-nucleotide polymorphism; MDACC, The University of Texas MD Anderson Cancer Center; NHS, the Nurse Health Study; HPFS, the Health Professionals Follow-up Study; NRG, number of risk genotypes; HR, hazards ratio; CI, confidence interval.

http://dx.doi.org/10.21037/atm-20-2117

Supplementary Table S4. Function prediction of independent SNPs and high linkage disequilibrium (LD) ($r^2 \geq 0.8$) associated with them in the peroxisome pathway

SNP	Chr	Gene	RegDB[a]	Haploreg v4.1[b]								
				LD (r^2)	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	GRASP QTL hits	Selected eQTL hits	dbSNP func annot
rs542279	11	*TMEM135*	6	0.81		4 tissues			5 altered motifs			intronic
rs631930	11	*TMEM135*	6	0.81		STRM			RFX5	1 hit		intronic
rs520718	11	*TMEM135*	No data	0.81					AIRE, ZID			intronic
rs556724	11	*TMEM135*	5	0.81		8 tissues	9 tissues					intronic
rs605658	11	*TMEM135*	5	0.81		10 tissues			Hmx, Nkx2, Nkx3			intronic
rs618159	11	*TMEM135*	5	0.81		5 tissues	4 tissues		Pax-4	1 hit		intronic
rs2847352	11	*TMEM135*	No data	0.85		GI			HNF4			intronic
rs498059	11	*TMEM135*	6	0.85					17 altered motifs			intronic
rs578116	11	*TMEM135*	No data	0.85		SKIN, BRN			GR, Irf			intronic
rs482944	11	*TMEM135*	4	0.85		STRM, SKIN, PANC	BRN, VAS		Bcl6b, Irx, Sp100			intronic
rs34782550	11	*TMEM135*	5	0.85		STRM, SKIN, PANC			4 altered motifs			intronic
rs34806361	11	*TMEM135*	6	0.85		STRM, SKIN, PANC			12 altered motifs			intronic
rs500725	11	*TMEM135*	No data	0.85								intronic
rs493708	11	*TMEM135*	No data	0.85		GI	BLD		NF-Y, Pbx3			intronic
rs139109823	11	*TMEM135*	No data	0.85		STRM, GI			4 altered motifs			intronic
rs567403	11	*TMEM135*	5	1		4 tissues		CFOS, CJUN, JUND	Dobox4, Irf		1 hit	intronic
rs7139158	12	*PEX5*	5	0.86		GI			4 altered motifs		54 hits	intronic
rs10743271	12	*PEX5*	No data	0.98					Foxp1		52 hits	intronic
rs10161405	12	*PEX5*	6	0.98					GATA, Pou3f2, TAL1		53 hits	intronic
rs10161542	12	*PEX5*	6	0.98					9 altered motifs		53 hits	intronic
rs3816424	12	*PEX5*	6	0.98		MUS			BHLHE40, Foxm1	3 hits	53 hits	intronic
rs10161170	12	*PEX5*	No data	0.99							58 hits	intronic
rs11044901	12	*PEX5*	No data	0.99					Pax-5, SP1		52 hits	intronic
rs10161103	12	*PEX5*	6	0.99					4 altered motifs	1 hit	51 hits	intronic
rs7969508	12	*PEX5*	1f	1	ESDR	ESDR	IPSC, OVRY			6 hits	53 hits	intronic
rs7969635	12	*PEX5*	5	1							52 hits	intronic
rs7969751	12	*PEX5*	6	1					8 altered motifs		54 hits	intronic

[a] RegulomeDB (http://www.regulomedb.org); [b] HaploReg v4.1 (http://archive.broadinstitute.org/mammals/haploreg/haploreg.php). Abbreviations: SNP, single-nucleotide polymorphism; Chr, chromosome; dbSNP funcannot, dbSNP function annotation.

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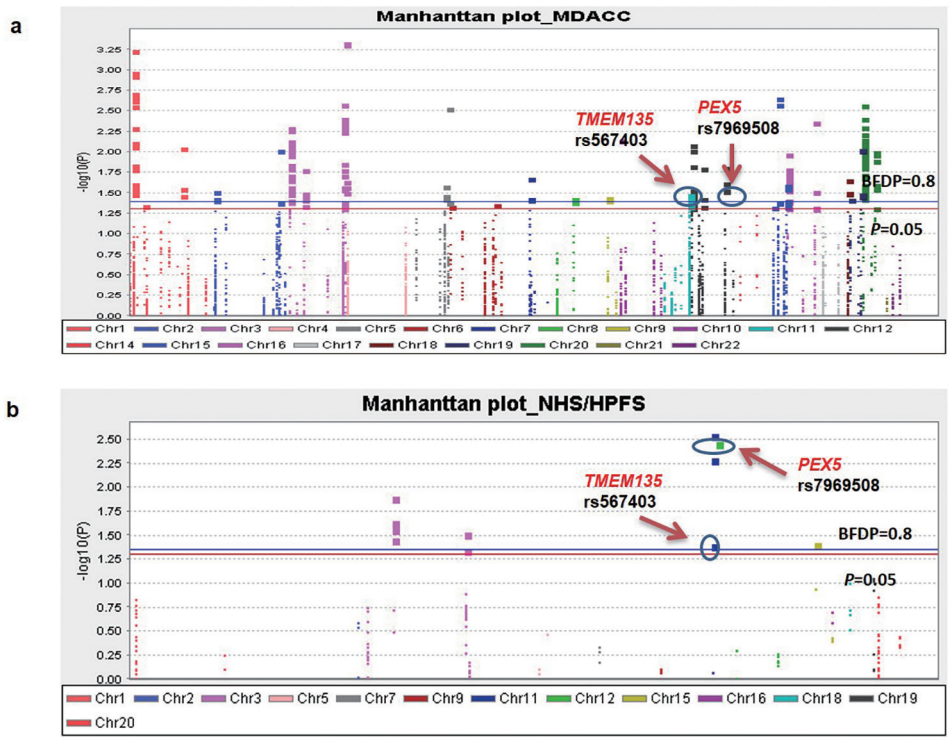
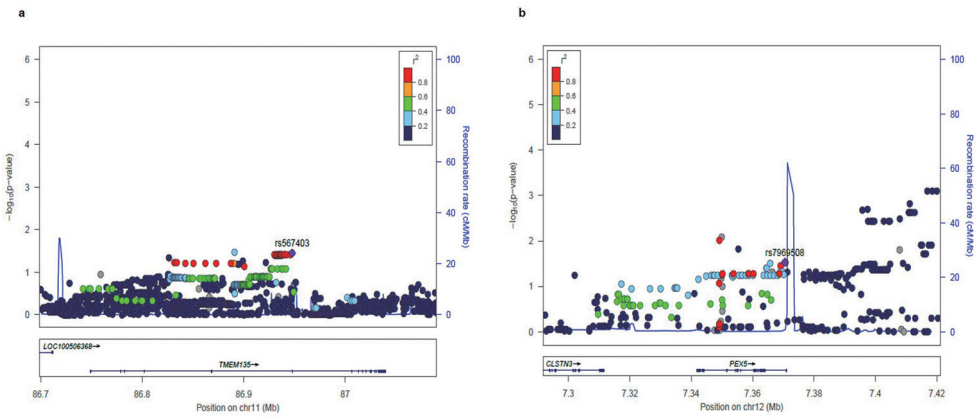
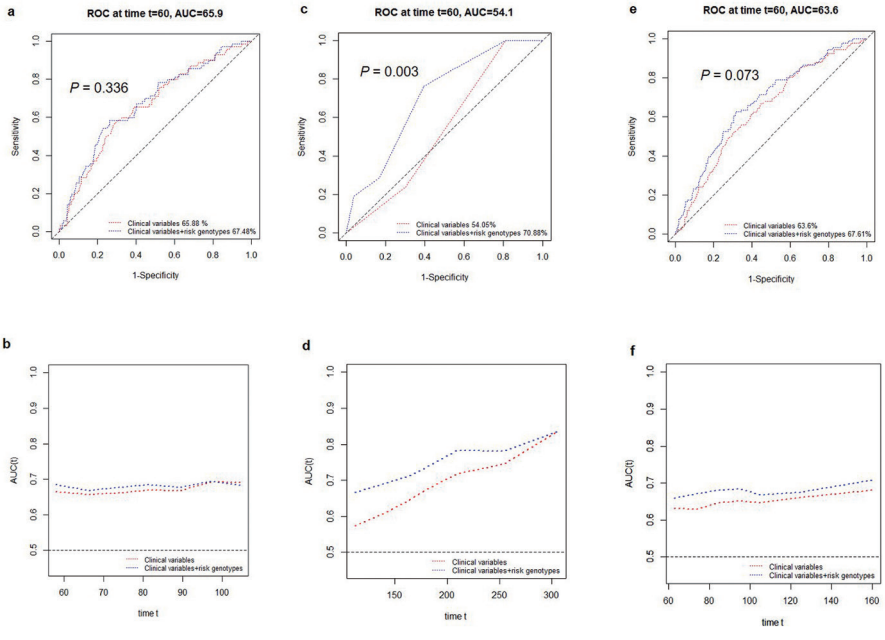


Supplementary Figure S1. Manhattan plot. (a) Manhattan plot for 8,397 SNPs in the MDACC study. There were 332 SNPs with P < 0.05 and 277 SNPs with BFDP < 0.8. (b) Manhattan plot for 277 SNPs in the NHS/HPFS study. The red horizontal line indicates P-value equal to 0.05 and the blue horizontal line represents a BFDP value equal to 0.8. Abbreviations: BFDP, Bayesian false-discovery probability; MDACC, The University of Texas MD Anderson Cancer Center; SNP, single nucleotide polymorphism; NHS, the Nurse Health Study; HPFS, the Health Professionals Follow-up Study; *PEX5*, peroxisomal biogenesis factor 5; *TMEM135*, transmembrane protein 135.



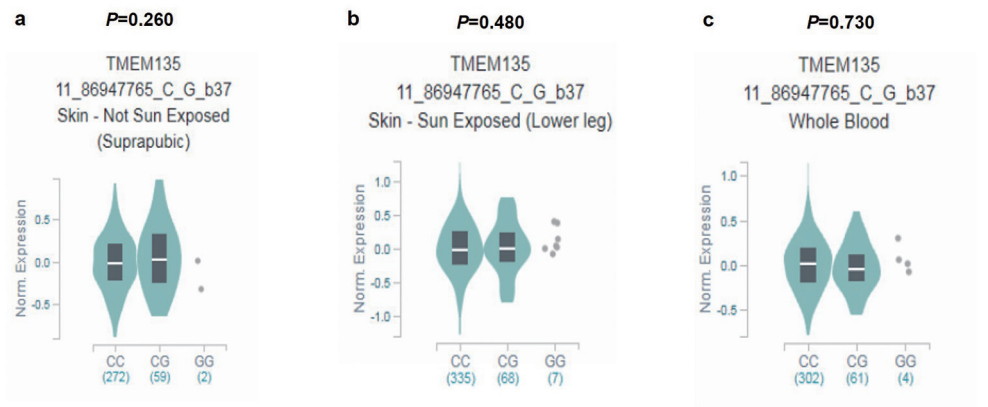
Supplementary Figure S2. Regional association plots showing 50 kb upstream and downstream of the gene regions in (a) *TMEM135* and (b) *PEX5*. Abbreviations: *PEX5*, peroxisomal biogenesis factor 5; *TMEM135*, transmembrane protein 135.



Supplementary Figure S3. The 5-year CMSS predicted by ROC curves in the (a) MDACC dataset, (c) NHS/HPFS dataset, and (e) the combined dataset. Time-dependent AUC estimation based on clinical variables in the (b) MDACC dataset, (d) NHS/HPFS dataset, and (f) the combined dataset. Abbreviations: CMSS, cutaneous melanoma-specific survival; ROC, receiver operating characteristic; MDACC, The University of Texas MD Anderson Cancer Center; NHS, the Nurse Health Study; HPFS, the Health Professionals Follow-up Study; AUC, area under ROC curve.

http://dx.doi.org/10.21037/atm-20-2117

Supplementary Figure S4. Functional prediction of SNPs in the ENCODE project. (a) Location and functional prediction of SNP rs567403. (b) Location and functional prediction of SNP rs7969508. Abbreviations: SNP, single nucleotide polymorphism; *PEX5*, peroxisomal biogenesis factor 5; *TMEM135*, transmembrane protein 135.



Supplementary Figure S5. The expression quantitative trait loci (eQTL) analysis for TMEM135 rs567403 in GTEx in (a) unexposed skin, (b) sun-exposed skin (lower leg), and (c) whole blood cells. Abbreviations: GTEx, Genotype-Tissue Expression Project; *TMEM135*, transmembrane protein 135.

http://dx.doi.org/10.21037/atm-20-2117