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Toll-like receptors and microbial exposure: gene-gene and gene-environment interaction in the development of atopy

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Multi Dimensionality Reduction (MDR)

MDR is a method that reduces dimensionality of multifactor information and aims to improve the identification of multiple factors associated with disease, i.e. MDR reduces multifactor information into one dimension, i.e. high risk versus low risk. MDR reports the performance of (combinations of) SNPs that represent the best predictor model for each number (e.g. 2 or 3) combinations (in our case genotypes and environmental factors). The dataset is divided into a training set (9/10 of the data) and a testing set (1/10 of the data). The best predictor model is the model with the lowest prediction error in the training set. The prediction error is $1 - \text{prediction accuracy}$. The prediction accuracy is the accuracy of the classification of cases and controls in the testing dataset calculated as $(\text{sensitivity} + \text{specificity})/2$. This procedure is repeated 10 times in the dataset. Cross-validation consistency is the number of times the combination is selected as best predictor model in the 10 times the data is analysed. Missing data were imputed for missing genotypes by multiple imputations using the Multivariate Imputation by Chained Equations (Mice) procedure that runs under the statistical program R version 2.4.1. After 100 imputations, convergence was achieved resulting in 5 imputed datasets. The model with the highest cross validation consistency and lowest prediction error in the 5 imputed datasets was selected as “best model”. P-values to evaluate the significance of each model were estimated via permutation testing, in which the null-hypothesis was rejected when the one-sided p-value, as estimated by 1000 permutations in Monte Carlo simulation, was below 5%. In that case the “best model” predicts the status of cases and controls better than chance without the need to correct for multiple testing.

Table 1

Gene nomenclature, location, ligand and heterodimer formation.

Gene	Full name	Location	Ligand(1)	Forms heterodimer with ¹
<i>TLR1</i>	Toll like receptor 1	4p14	Bacteria and mycobacteria	TLR2
<i>TLR2</i>	Toll like receptor 2	4q32	Gram-positive bacteria, virus and Fungi (a.o. B-glycan)	TLR1 ,6
<i>TLR3</i>	Toll like receptor 3	4q35	Viruses	
<i>TLR4</i>	Toll like receptor 4	9q32	Gram-negative bacteria, respiratoir syncitial virus	
<i>TLR5</i>	Toll like receptor 5	1q41	Bacteria	
<i>TLR6</i>	Toll like receptor 6	4p14	Mycoplasma, gram-positive bacteria	TLR2
<i>TLR9</i>	Toll like receptor 9	3p21	Bacteria and viruses	
<i>TLR10</i>	Toll like receptor 10	4p14	Unknown	
				Interacts with ²⁻⁴
<i>CD14</i>		5q31	Lipopolysaccharide, viruses, poly I:C	TLR2, 3, 4, TLR2/6 heterodymer
<i>MD2</i>	Myeloid differentiation protein-2	8q21	Forms complex with CD14 and TLR4	TLR4
<i>LBP</i>	Lipopolysaccharide Binding Protein	20q11	Lipopolysaccharide	TLR4
<i>Dectin-1</i>	Dendritic cell-associated C-type lectin	12p13	Fungi (B-glycan)	TLR2

Table 2

List of selected SNPs. (including Snps of special interest due to previous associations or functionality (see references) forced in as a tag SNP)

SNP	Chromosomal position	Alleles	GENE	Minor Allele frequency	Call rate (%)
rs1039559	38831596	T/C	<i>TLR6</i>	46.3	96.4
rs10759931*	120464147	C/T	<i>TLR4</i>	43.3	97.0
rs10759932	120465144	T/C	<i>TLR4</i>	13.0	96.5
rs10808798	74906514	T/C	<i>MD2</i>	47.3	97.5
rs10856839	38777236	A/C	<i>TLR10</i>	17.5	97.5
rs11096956 ⁵	38776180	G/T	<i>TLR10</i>	20.2	96.2
rs11096957	38776491	A/C	<i>TLR10</i>	36.1	97.0
rs11466652	38776303	A/G	<i>TLR10</i>	15.1	97.5
rs11536878	120471553	C/A	<i>TLR4</i>	12.1	97.0
rs11536889	120478131	G/C	<i>TLR4</i>	13.9	97.7
rs11536945	36979832	G/A	<i>LBP</i>	24.0	98.5
rs11536949	36985885	G/T	<i>LBP</i>	07.1	99.0
rs11536988	37000937	T/A	<i>LBP</i>	04.4	98.6
rs11721827	186991137	A/C	<i>TLR3</i>	15.0	98.0
rs11786591	74916344	C/T	<i>MD2</i>	32.9	96.6
rs12829123	10273166	A/G	<i>DECTIN1</i>	45.2	95.5
rs13126816	186994178	G/A	<i>TLR3</i>	23.1	98.1
rs16938758	74919749	A/T	<i>MD2</i>	18.5	97.2
rs17226566	74919912	T/C	<i>MD2</i>	23.5	97.6
rs1780616	36972942	C/T	<i>LBP</i>	33.3	96.7
rs187084	52261031	T/C	<i>TLR9</i>	42.1	97.0
rs1898830	154608453	A/G	<i>TLR2</i>	34.4	96.8
rs1927911	120470054	C/T	<i>TLR4</i>	25.5	92.6
rs2072493*	10276562	C/T	<i>TLR5</i>	14.7	97.1
rs2078178	10276562	C/T	<i>DECTIN1</i>	24.7	97.4
rs2232596	36989381	A/G	<i>LBP</i>	49.9	96.6
rs2241096	223310048	C/T	<i>TLR5</i>	09.6	97.6
rs2563298	140011315	C/A	<i>CD14</i>	27.3	98.3
rs2569190 ⁶	140012916	G/A	<i>CD14</i>	47.9	97.6
rs2569191 ⁶	140013903	T/C	<i>CD14</i>	48.2	98.3
rs2770150	120463139	T/C	<i>TLR4</i>	26.6	96.8
rs2915863 ⁶	140014377	T/C	<i>CD14</i>	40.5	94.4
rs352140 ⁵	52256697	T/C	<i>TLR9</i>	44.5	97.5
rs3775291	187004074	G/A	<i>TLR3</i>	28.6	97.6

rs3775292	187003025	C/G	<i>TLR3</i>	20.9	97.2
rs3775296	186997767	G/T	<i>TLR3</i>	18.7	96.2
rs3804099 ⁷	154624656	T/C	<i>TLR2</i>	44.1	96.8
rs3804100 ⁷	154625409	T/C	<i>TLR2</i>	6.6	97.9
rs4129009 ⁵	38774889	A/G	<i>TLR10</i>	17.2	98.0
rs4274855	38777471	G/A	<i>TLR10</i>	17.2	97.5
rs4696480 ⁷	154607126	T/A	<i>TLR2</i>	49.1	98.0
rs4986790 ^{7,8}	120475302	A/G	<i>TLR4</i>	07.0	98.2
rs4986791 ^{7,8}	120475602	C/T	<i>TLR4</i>	07.1	98.0
rs5741812	36973999	A/T	<i>LBP</i>	12.8	97.4
rs5743557	38806827	C/T	<i>TLR1</i>	17.6	97.9
rs5743594	38802751	C/T	<i>TLR1</i>	18.9	99.0
rs5743604	38801285	T/C	<i>TLR1</i>	23.1	98.3
rs5743618	38798648	G/T	<i>TLR1</i>	28.4	98.0
rs5743788	38833207	C/G	<i>TLR6</i>	49.1	98.2
rs5743798	38832374	C/T	<i>TLR6</i>	27.3	95.6
rs5743810	38830350	C/T	<i>TLR6</i>	40.8	96.7
rs5743836 ⁵	52260782	T/C	<i>TLR9</i>	14.2	98.0
rs5744105	223316077	C/G	<i>TLR5</i>	49.5	97.1
rs5744109	223315480	T/C	<i>TLR5</i>	09.3	97.8
rs5744157	223306976	C/G	<i>TLR5</i>	11.8	98.3
rs574416	223285200	C/T	<i>TLR5</i>	6.6	98.1
rs5744455 ⁶	140013307	C/T	<i>CD14</i>	23.1	96.6
rs6025083	36979787	T/C	<i>LBP</i>	45.2	96.8
rs6478317	120464181	A/G	<i>TLR4</i>	34.8	98.3
rs6531666	38832168	T/C	<i>TLR6</i>	31.6	91.3
rs745144	37005536	C/T	<i>LBP</i>	43.2	97.6
rs7657186	186994039	G/A	<i>TLR3</i>	21.3	96.7
rs7668666	187001292	C/A	<i>TLR3</i>	26.3	96.7
rs7838114	74935611	G/A	<i>MD2</i>	19.2	97.6
rs7959451	10271055	C/T	<i>DECTIN1</i>	14.7	96.3

*SNPs did not pass Hardy Weinberg equilibrium

Table 3

Single SNP analysis.

Odds ratios and 95% CI are shown (only significant ($p \leq 0.05$) SNPs are shown)

Gene	Rs number	Total IgE 1-2 yrs	Total IgE 6-8 yrs	Specific IgE Indoor Allergens 6-8 yrs
<i>CD14</i>	rs2569190		1.5 (1.0-2.3) R	
<i>LBP</i>	rs745144		1.6 (1.1-2.3) D	
<i>LY96</i>	rs7838114	0.4 (0.2-0.9) R		
<i>LY96</i>	rs10808798	0.7 (0.6-1.0) D		
<i>TLR1</i>	rs5743594			3.9(2.0-8.1) R
<i>TLR1</i>	rs5743618			0.5(0.3-1.0) R
<i>TLR1</i>	rs5743604			0.6(0.5-0.9) D
<i>TLR2</i>	rs1898830		1.4(1.0-2.0) D	
<i>TLR2</i>	rs4696480		0.6(0.4-0.9) R	
<i>TLR3</i>	rs3775296		0.7(0.5-1.0) D	
<i>TLR3</i>	rs7657186	1.4(1.1-1.8) H		
<i>TLR4</i>	rs2770150		2.0 (1.1-3.8) R	
<i>TLR4</i>	rs6478317			
<i>TLR4</i>	rs1927911		0.7(0.5-0.0) D	
<i>TLR6</i>	rs5743810			1.8(1.2-2.7) R
<i>TLR6</i>	rs1039559	0.7(0.5-0.9) H		
<i>TLR6</i>	rs5743798			1.4(1.0-1.9) D
<i>TLR6</i>	rs6531666	1.5(1.0-2.2) R		
<i>TLR10</i>	rs4274855			0.3(0.1-0.9) R
<i>TLR10</i>	rs10856839	2.0(1.0-2.9) R		
<i>TLR10</i>	rs11466652	2.3(1.0-5.1) R		
<i>TLR10</i>	rs11096956			0.4(0.1-0.9) R
<i>TLR10</i>	rs4129009			0.2(0.1-0.8) R
<i>TLR10</i>	rs11096957			0.7(0.5-0.9) D

D:Dominant model, R:Recessive model; H:Heterozygote compared to minor allele.

There is overlapping data in this table with the article "TLR-related pathway analysis: novel gene-gene interactions in the development of asthma and atopy" Reijmerink NE, Bottema RW, Kerkhof M Allergy. 2010 Feb;65(2):199-207

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