Online supplement to Gene Expression Pathways across Multiple Tissues in Antineutrophil Cytoplasmic Antibody-associated Vasculitis Reveal Core Pathways of Disease Pathology, *The Journal of Rheumatology*, doi:10.3899/jrheum.180455

Supplement A. Local false discovery rate (locfdr) in one dimension

A local false discovery rate (locfdr) is defined from a mixture of distributions. Suppose that we have k tests each with p-value p_i, for $i = 1, 2, \dots, k$. Let z be the test statistic of interest (pathways in the manuscript). Each case (or test) can be considered from either null (H0) or alternative (H1) with the prior probabilities of

p_0 = probability(H0) and p_1 = probability(H1) = $1 - p_0$.

Then, z values have the following mixture density

$f(z) = p_0 f_0(z) + p_1 f_1(z)$,

where $f_0(z)$ and $f_1(z)$ are the null and alternative densities, respectively.

Then, the locfdr is defined as $locfdr(z) = probability\{H0 \mid Z=z\}$, where Z is a test statistic. Under the mixture model above, it is straightforward to show (S1, S2)

$locfdr(z) = p_0 f_0(z) / f(z)$.

There can be several different choices of f_0 and f_1, and ways to estimate them. In our approach, f_0 is a normal distribution and f_1 is a log-concave density function. Then, we estimate p_0, f_0 and f_1 by the EM algorithm that is most widely used to estimate a mixture density.

The above is the description of one-dimensional case and the technical report (S1) presents the extension to multi-dimensional cases and simulation studies to show how well our approach can estimate locfdr under various settings and performs better than other existing methods.

References:

S1. Jeong S-O, Choi, D., Jang, W. A semiparametric mixture method for local false discovery rate estimation. Arxivorg 2016;Available from: http://arxiv.org/abs/1604.04264.

s2. Efron B. Microarrays, empirical bayes and the two-groups model. Statist Sci 2008;23:1-22.

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Supplementary Table 1: Individual genes associated with AAV pathways.

Pathway	**Peripheral leukocyte genes**	**Nasal sinus brushing genes**	**Orbital tissue genes**	**md-locfdr***
Innate Immunity				
Neutrophil degranulation(R)	*SLC11A1,SLPI,RAB5C, S100A12,DEFA4,VNN 1,TCN1,LCN2,TNFAIP 6,PYGL,HK3,CAMP,SE RPINB1,ARG1,NFAM 1,MMP9,CKAP4,CEAC AM8,LTF,TLR2,CD59, MAPK14,LRG1,QPCT, PTX3*	*GMFG,C3AR1,SLC11A 1,FPR1,FPR2,S100A12, CD14,SIGLEC9,SERPIN A1,HBB,MMP25,TIMP 2,OLR1,CD53,FCER1G, MME,TLR2,CXCR1,AL OX5,CXCR2,LILRB2,LIL RB3,QPCT,SIGLEC5,PL AU,COTL1,CD93,CD30 0A,CLEC4D,TYROBP,A DAM8,S100A9,S100A 8,C5AR1,HSPA6,PTPR C,SELL,ITGAM,TNFAIP 6,ITGB2,LRMP,FCAR,IT GAX,CR1,PLAUR,TNFR SF1B,MMP9,FGR,CHI3 L1,DOCK2,FCGR2A,M NDA*	*FCN1,CLEC5A,SL C11A1,CLEC4D,A DAM8,LYZ,ARHG AP9,SERPINA1,IT GB2,TCIRG1,SLC2 A5,ITGAL,SIRPB1, ITGAX,KCNAB2, MMP9,CHI3L1,TL R2,LILRA3,ALOX5*	$1.05x10^{-12}$
	$p=3.14x10^{-13}$	$p= 1.11x10^{-16}$	$p=3.28x10^{-09}$	
Antimicrobial peptides(R)	*SLC11A1,DEFA4,LCN2 ,CAMP,LTF,TLR2*	*SLC11A1,TLR2,S100A9 ,S100A8,DEFA3*	*SLC11A1,LYZ,CCR 2,TLR2*	$8.23x10^{-03}$
	$p=7.69x10^{-06}$	$p=1.13x10^{-03}$	$p=1.14x10^{-03}$	
Toll-Like Receptors Cascades(R)	*MEF2A,LY96,S100A1 2,PELI1,TLR10,TLR5,T LR2,MAPK3,MAPK14*	*S100A12,CD14,FOS,TL R8,TLR4,TLR2,S100A9, S100A8,ITGAM,ITGB2*	*RPS6KA1,ITGB2,I KBKE,TLR8,TLR2, PTPN11*	0.026
	$p=1.85x10^{-05}$	$p=2.78x10^{-04}$	$p=3.39x10^{-03}$	
Phagosome(K)	*RAB5C,TLR2*	*CD14,OLR1,TLR4,TLR2 ,NCF2,NCF4,CORO1A, CLEC7A,ITGAM,ITGB2,*	*COMP,CLEC7A,IT GB2,TCIRG1,TLR 2*	$3.17x10^{-03}$

		FCAR,FCGR3A,ITGA5,THBS1,FCGR2A,FCGR2B		
	p=0.477	p=2.88x10^{-08}	p=0.021	
Interferon gamma signaling(R)	*SOCS3*	*SOCS3*	*CIITA,IRF8,PTPN1,PTPN11*	0.134
	p=0.533	p=0.733	p=6.9x10^{-03}	
Adaptive Immunity				
Signaling by the B Cell Receptor (BCR)(R)	*IRS2,MAPK3*	*PRKCB,EREG,HBEGF*	*IER3,ITPR1,DAPP1,IGHM,IGLC1,IGHD,IGKC,PTPN11*	0.022
	p=0.774	p=0.867	p=6.68x10^{-03}	
Vascular wall interactions				
Cell surface interactions at the vascular wall(R)	*CEACAM8*	*FN1,OLR1,FCER1G,SLC7A5,SELPLG,SELL,ITGAM,ITGB2,TREM1,THBD,ITGAX,ITGA5*	*CD84,SLC16A3,FN1,IGHM,ITGB2,ITGAL,ITGAX,IGLC1,IGKC,PTPN11*	4.19x10^{-04}
	p=0.887	p=4.49x10^{-04}	p=5.86x10^{-05}	
amb2 Integrin signaling(N)	MMP9	HCK,SELPLG,PLAT,PLAU,ITGAM,ITGB2,MMP9	ITGB2,MMP9	0.086
	p=0.276	p=1.90x10^{-06}	p=0.041	
Leukocyte transendothelial migration(K)	*MMP9,MAPK14*	*PRKCB,PIK3R5,RAC2,CXCR4,NCF2,NCF4,ITGAM,ITGB2,MMP9*	*ITGB2,ITGAL,MMP9,CXCR4,PTPN11*	0.178
	p=0.34	p=2.94x10^{-04}	p=6.98x10^{-03}	
Cellular signaling				
Signaling by Interleukins(R)	*IL1RN,IRS2,IL18RAP,IL1R1,IL1R2,CSF2RA,R*	*IL1RN,IL36A,JUNB,IL1R2,EREG,FPR1,FN1,IL3*	*IL1RN,IGHG1,FN1,IL7R,ITGB2,ITG*	6.13x10^{-04}

	ASGRP4,SOCS3,LCN2, RASGEF1A,MMP9,PE LI1,MAPK3,OSM,IL18 R1	*6G,FOS,IL1B,HBEGF,P TGS2,ALOX5,IL10RA,O SM,CSF3R,IL18RAP,CS F2RB,RASGRP4,SOCS3, ITGAM,ITGB2,ITGAX,T NFRSF1B,MMP9,CCL4, CCL3*	*AX,JAK3,CCR2,M MP9,IL17RA,CCL 11,IL2RG,ALOX5, CCL19,IL12RB1,P TPN11*	
	$p=8.91x10^{-05}$	$p=8.24x10^{-08}$	$p=1.88x10^{-05}$	
Cytokine-cytokine receptor interaction(K)	*CXCL16,IL18RAP,IL1R 1,IL1R2,CSF2RA,FLT1, OSM,IL18R1*	*IL1R2,IL1B,CXCR4,CXC R1,CXCR2,CCL18,CCL2 4,IL10RA,OSM,CSF3R, CXCL13,IL18RAP,CSF2 RB,TNFRSF10C,TNFRS F1B,CCL4,CCL3*	*IL7R,CCR2,IL17R A,LTB,CCL11,CXC R4,IL2RG,IL21R,C CL19,IL12RB1*	0.036
	$p=6.66x10^{-03}$	$p=7.78x10^{-06}$	$p=4.08x10^{-04}$	
Chemokine signaling pathway(K)	*CXCL16,WAS,MAPK3*	*PREX1,PRKCB,PIK3R5, RAC2,HCK,CXCR4,CXC R1,CXCR2,CCL18,CCL2 4,CXCL13,FGR,DOCK2, CCL4,CCL3*	*GRK6,JAK3,CCR2, CCL11,CXCR4,CC L19*	0.041
	p=0.308	$p=1.97x10^{-06}$	p=0.013	
IL4-mediated signaling events(N)	*SPI1,IRS2,SOCS3,ARG 1,MAPK14*	*SPI1,EGR2,SOCS3*	*IGHG1,HMGA1,J AK3,CCL11,IL2RG*	0.021
	$p=5.47x10^{-04}$	p=0.107	$p=5.04x10^{-04}$	
Complement Activation				
Complement and coagulation cascades(K)	*F5,CD59*	*C3AR1,SERPINA1,PLAT ,PLAU,C5AR1,ITGAM,I TGB2,THBD,ITGAX,CR 1,PLAUR*	*SERPINA1,ITGB2, ITGAX*	0.044
	p=0.199	$p=2.70x10^{-07}$	p=0.048	
Tissue Damage/Tissue Repair				
Urokinase-type plasminogen	*MMP9*		*FN1,ITGB2,MMP 9*	$7.77x10^{-03}$

activator (uPA) and uPAR-mediated signaling(N)		*FPR1,FPR2,FN1,PLAU,ITGAM,ITGB2,PLAUR,MMP9,ITGA5*		
	p=0.354	$p=9.81x10^{-08}$	$p=9.39x10^{-03}$	
Extracellular matrix organization(R)	*COL9A2,MMP9,CEACAM8*	*SPARC,ICAM3,KLK7,FN1,TIMP2,SPP1,ADAM8,ITGAM,ITGB2,ITGAX,MMP9,ITGA5,THBS1,LUM*	*DMP1,COMP,ADAM8,FN1,ITGB2,ITGAL,ITGAX,MMP9,SPP1*	0.024
	p=0.497	$p=2.51x10^{-04}$	$p=1.27x10^{-03}$	
Platelet Activation				
Response to elevated platelet cytosolic Ca2+(R)	*F5*	*SPARC,PRKCB,CD109,FN1,FERMT3,ECM1,SERPINA1,FLNA,PLEK,SRGN,THBS1*	*STXBP2,FN1,SERPINA1*	0.038
	p=0.670	$p=4.50x10^{-06}$	p=0.095	
GPVI-mediated activation cascade(R)	*CSF2RA*	*PIK3R5,RAC2,FCER1G,CSF2RB,LCP2*	*JAK3,IL2RG,PDPN,PTPN11*	0.079
	p=0.400	$p=2.1x10^{-03}$	$p=1.69x10^{-03}$	
Platelet homeostasis(R)	*SLC8A1,MRVI1,MAPK14*	*FGR*	*SLC8A1,ITPR1,ATP2A3,PTPN11*	0.091
	p=0.024	p=0.656	$p=3.28x10^{-03}$	
Infectious Disease Pathways				
Leishmaniasis(K)	*TLR2,MAPK3,MAPK14*	*PRKCB,FOS,IL1B,TLR4,TLR2,PTGS2,NCF2,NCF4,ITGAM,ITGB2,FCGR3A,CR1,FCGR2A*	*ITGB2,TLR2*	$3.54x10^{-03}$
	p=0.041	$p=1.22x10^{-09}$	p=0.172	
Malaria(K)	*TLR2*	*HBB,HBA1,IL1B,TLR4,TLR2,ITGB2,CR1,THBS1*	*COMP,ITGB2,ITGAL,TLR2*	0.012
	p=0.400	$p=3.77x10^{-06}$	$p=1.69x10^{-03}$	

Tuberculosis(K)	*RAB5C,CAMP,TLR2,MAPK3,MAPK14*	*CD14,PLK3,FCER1G,IL1B,TLR4,TLR2,IL10RA,CLEC4E,CORO1A,CLEC7A,ITGAM,ITGB2,FCGR3A,ITGAX,CR1,FCGR2A,FCGR2B*	*CLEC7A,VDR,CIITA,ITGB2,TCIRG1,ITGAX,TLR2*	0.019
	p=0.040	$p=3.79x10^{-08}$	$p=2.52x10^{-03}$	
Measles(K)	*TLR2*	*PIK3R5,IL1B,TLR4,TLR2,HSPA6,TNFRSF10C,FCGR2B*	*SLAMF1,SH2D1A,JAK3,IKBKE,TLR2,IL2RG*	0.035
	p=0.759	p=0.012	$p=2.84x10^{-03}$	
Amoebiasis(K)	*IL1R1,IL1R2,RAB5C,SERPINB1,ARG1,TLR2*	*PRKCB,IL1R2,PIK3R5,CD14,FN1,IL1B,TLR4,TLR2,ITGAM,ITGB2*	*FN1,ITGB2,TLR2*	0.142
	$p=5.97x10^{-04}$	$p=1.42x10^{-05}$	p=0.080	
Other				
Osteoclast differentiation(K)	*SPI1,IL1R1,SOCS3,MAPK3,MAPK14*	*SPI1,JUNB,PIK3R5,FOS,IL1B,LILRA1,LILRA2,LILRA5,LILRB2,LILRB3,FOSB,NCF2,NCF4,TYROBP,SOCS3,FCGR3A,LCP2,FCGR2A,FCGR2B*	*SIRPB1,LILRA3**	$3.75x10^{-05}$
	p=0.013	$p=6.19x10^{-12}$	p=0.391	
Inflammatory bowel disease (IBD)(K)	*IL18RAP,TLR5,TLR2,IL18R1*	*IL1B,TLR4,TLR2,IL18RAP*	*FOXP3,TLR2,IL2RG,IL21R,IL12RB1*	0.093
	$p=4.91x10^{-03}$	p=0.031	$p=5.8x10^{-04}$	
Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds(R)	*SLC11A1,SLC22A4,SLC40A1,SLC18A2*	*SLC11A1*	*SLC16A3,SLC11A1,SLC2A5*	0.124
	$p=1.12x10^{-03}$	p=0.540	p=0.01	

Syndecan-4-mediated signaling events(N)	*MMP9*	*FN1,CXCR4,MMP9,ITGA5,THBS1*	*FN1,MMP9,CXCR4*	0.155
	p=0.283	$p=3.18x10^{-04}$	$p=4.47x10^{-03}$	

*md-localFDR = multi-dimensional local false discovery rate, which can be thought of as the probability of individual pathway being a false discovery in *all three* tissues.

C = CellMap, R = Reactome, K = Kyoto Encyclopedia of Genes and Genomes (KEGG), N = National Cancer

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Supplementary Table 2: Downregulated pathways associated with two out of three tissues.		
Orbit and nasal sinus brushings	**Orbit and leukocytes**	**Nasal sinus brushings and leukocytes**
Metabolism of xenobiotics by cytochrome P450(K) Orbit p=2.40x10^{-03}, FDR=0.077 Nasal p=2.00x10^{-04}, FDR=5.20x10^{-03}	Cytokine-cytokine receptor interaction(K) Orbit p=0.069, FDR=0.162 Leukocyte p=3.05x10^{-04}, FDR=8.53x10^{-03}	IL12-mediated signaling events(N) Nasal p=0.091, FDR=0.113 Leukocyte p=8.68x10^{-03}, FDR=0.069
Drug metabolism - cytochrome P450(K) Orbit p=0.026, FDR=0.162 Nasal p=1.70x10^{-04}, FDR=5.20x10^{-03}	Response to elevated platelet cytosolic Ca2+(R) Orbit p=6.53x10^{-03}, FDR=0.127 Leukocyte p=0.217, FDR=0.217	NOD-like receptor signaling pathway(K) Nasal p=0.235, FDR=0.235 Leukocyte p=0.058, FDR=0.117
Tyrosine metabolism(K) Orbit p=7.10x10^{-03}, FDR=0.127 Nasal p=0.053, FDR=0.113	Caspase cascade in apoptosis(N) Orbit p=0.171, FDR=0.171 Leukocyte p=6.38x10^{-03}, FDR=0.060	Chagas disease (American trypanosomiasis)(K) Nasal p=0.011, FDR=0.091 Leukocyte p=0.214, FDR=0.214
Retinol metabolism(K) Orbit p=0.209, FDR=0.209 Nasal p=1.37x10^{-04}, FDR=5.20x10^{-03}	Malaria(K) Orbit p=0.162, FDR=0.162 Leukocyte p=0.107, FDR=0.117	Pathways in cancer(K) Nasal p=0.126, FDR=0.126 Leukocyte p=0.062, FDR=0.117
Chemical carcinogenesis(K) Orbit p=0.035, FDR=0.162 Nasal p=2.70x10^{-04}, FDR=5.67x10^{-03}	Signaling events mediated by PTP1B(N) Orbit p=0.015, FDR=0.162 Leukocyte p=0.113, FDR=0.117	Signaling by Interleukins(R) Nasal p=0.160, FDR=0.160 Leukocyte p=0.087, FDR=0.117
Steroid hormone biosynthesis(K) Orbit p=0.188, FDR=0.188 Nasal p=3.67x10^{-03}, FDR=0.029	Adherens junction(K) Orbit p=0.228, FDR=0.228 Leukocyte p=0.153, FDR=0.153	Cytosolic DNA-sensing pathway(K) Nasal p=0.096, FDR=0.113 Leukocyte p=0.137, FDR=0.137
Fatty acid degradation(K) Orbit p=0.146, FDR=0.162 Nasal p=0.067, FDR=0.113	Viral myocarditis(K) Orbit p=0.191, FDR=0.191 Leukocyte p=0.127, FDR=0.127	Circadian entrainment(K) Nasal p=0.14, FDR=0.14 Leukocyte p=0.199, FDR=0.199
AP-1 transcription factor network(N) Orbit p=0.223, FDR=0.223	Integration of energy metabolism(R) Orbit p=0.043, FDR=0.162	Melanogenesis(K) Nasal p=0.147, FDR=0.147 Leukocyte p=0.208, FDR=0.208

Nasal p=0.104, FDR=0.113	Leukocyte p=0.192, FDR=0.192	
Phase 1 - Functionalization of compounds(R) Orbit p=0.031, FDR=0.162 Nasal p=0.113, FDR=0.113		Retrograde endocannabinoid signaling(K) Nasal p=0.147, FDR=0.147 Leukocyte p=0.208, FDR=0.208
Glycolysis / Gluconeogenesis(K) Orbit p=0.214, FDR=0.214 Nasal p=0.010, FDR=0.113		Cholinergic synapse(K) Nasal p=0.160, FDR=0.160 Leukocyte p=0.226, FDR=0.226
Signaling by Retinoic Acid(R) Orbit p=0.115, FDR=0.162 Nasal p=0.052, FDR=0.113		Serotonergic synapse(K) Nasal p=0.163, FDR=0.163 Leukocyte p=0.23, FDR=0.23
Long-term potentiation(K) Orbit p=0.214, FDR=0.214 Nasal p=0.010, FDR=0.113		Glutamatergic synapse(K) Nasal p=0.164, FDR=0.164 Leukocyte p=0.232, FDR=0.232
		Sphingolipid signaling pathway(K) Nasal p=0.172, FDR=0.172 Leukocyte p=0.242, FDR=0.242
R = Reactome, K = Kyoto Encyclopedia of Genes and Genomes (KEGG), N = National Cancer Institute Pathway Interaction Database (NCI PID), FDR = false discovery rate		