

HLA gene expression is altered in whole blood and placenta from women who later developed preeclampsia

Small H., Akehurst C., Sharafetdinova L., McBride M., McClure J., Robinson S., Carty D., Freeman D., Delles C.

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© The American Physiological Society. Preeclampsia is a multisystem disease that significantly contributes to maternal and fetal morbidity and mortality. In this study, we used a non-biased microarray approach to identify dysregulated genes in maternal whole blood samples which may be associated with the development of preeclampsia. Whole blood samples were obtained at 28 wk of gestation from 5 women who later developed preeclampsia (cases) and 10 matched women with normotensive pregnancies (controls). Placenta samples were obtained from an independent cohort of 19 women with preeclampsia matched with 19 women with normotensive pregnancies. We studied gene expression profiles using Illumina microarray in blood and validated changes in gene expression in whole blood and placenta tissue by qPCR. We found a transcriptional profile differentiating cases from controls; 336 genes were significantly dysregulated in blood from women who developed preeclampsia. Functional annotation of microarray results indicated that most of the genes found to be dysregulated were involved in inflammatory pathways. While general trends were preserved, only HLA-A was validated in whole blood samples from cases using qPCR (2.30 ± 0.9 -fold change) whereas in placental tissue HLA-DRB1 expression was found to be significantly increased in samples from women with preeclampsia (5.88 ± 2.24 -fold change). We have identified that HLA-A is upregulated in the circulation of women who went on to develop preeclampsia. In placenta of women with preeclampsia we identified that HLA-DRB1 is upregulated. Our data provide further evidence for involvement of the HLA gene family in the pathogenesis of preeclampsia.

<http://dx.doi.org/10.1152/physiolgenomics.00106.2016>

Keywords

Gene expression, Microarray, Placenta, Preeclampsia

References

- [1] Benjamini Y, Hochberg Y. Controlling the false discovery rate a practical and powerful approach to multiple testing. *J Roy Stat Soc B Met* 57: 289-300, 1995.
- [2] Burke SD, Karumanchi SA. Spiral artery remodeling in preeclampsia revisited. *Hypertension* 62: 1013-1014, 2013. doi:10.1161/HYPERTENSIONAHA.113.02049.
- [3] Capittini C, Pasi A, Bergamaschi P, Tinelli C, De Silvestri A, Mercati MP, Badulli C, Garlaschelli F, Sbarsi I, Guarene M, Martinetti M, Salvaneschi L, Cuccia M. HLA haplotypes and birth weight variation: is your future going to be light or heavy? *Tissue Antigens* 74: 156-163, 2009. doi:10.1111/j.1399-0039.2009.01282.x.

- [4] Carty DM, Siwy J, Brennand JE, Zürbig P, Mullen W, Franke J, McCulloch JW, Roberts CT, North RA, Chappell LC, Mischak H, Poston L, Dominiczak AF, Delles C. Urinary proteomics for prediction of preeclampsia. *Hypertension* 57: 561-569, 2011. doi:10.1161/HYPERTENSIONAHA.110.164285.
- [5] Chaiworapongsa T, Romero R, Whitten A, Tarca AL, Bhatti G, Draghici S, Chaemsaitong P, Miranda J, Hassan SS. Differences and similarities in the transcriptional profile of peripheral whole blood in early and late-onset preeclampsia: insights into the molecular basis of the phenotype of preeclampsia. *J Perinat Med* 41: 485-504, 2013. doi:10.1515/jpm-2013-0082
- [6] Coulam CB. Immunologic tests in the evaluation of reproductive disorders: a critical review. *Am J Obstet Gynecol* 167: 1844-1851, 1992. doi:10.1016/0002-9378(92)91785-9.
- [7] Dahlstrøm B, Esbensen Y, Vollan H, Oian P, Bukholm G. Genome profiles in maternal blood during early onset preeclampsia and towards term. *J Perinat Med* 38: 601-608, 2010. doi:10.1515/jpm.2010.095.
- [8] Dahlstrøm B, Romundstad P, Øian P, Vatten LJ, Eskild A. Placenta weight in pre-eclampsia. *Acta Obstet Gynecol Scand* 87: 608-611, 2008. doi:10.1080/00016340802056178.
- [9] Ding Y, Shen H, Wang X, Fan X, Wu X, Yang X. The polymorphism of HLA-DR and -DQ allelic genes associated with intrahepatic cholestasis of pregnancy. *Genet Test* 12: 215-220, 2008. doi:10.1089/gte.2007.0053
- [10] Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 330: 565-567, 2005. doi:10.1136/bmj.38380.674340.E0.
- [11] Gharesi-Fard B, Askarinejad-Behbahani R, Behdin S. The effect of HLA-DRB1 sharing between the couples with recurrent pregnancy loss on the pregnancy outcome after leukocyte therapy. *Iran J Immunol* 11: 13-20, 2014. JIv11i1A2
- [12] Hiby SE, Walker JJ, O'shaughnessy KM, Redman CWG, Carrington M, Trowsdale J, Moffett A. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J Exp Med* 200: 957-965, 2004. doi:10.1084/jem.20041214.
- [13] Hylenius S, Andersen AMN, Melbye M, Hviid TVF. Association between HLA-G genotype and risk of pre-eclampsia: a case-control study using family triads. *Mol Hum Reprod* 10: 237-246, 2004. doi:10.1093/molehr/gah035.
- [14] Kane S, Kisiel J, Shih L, Hanauer S. HLA disparity determines disease activity through pregnancy in women with inflammatory bowel disease. *Am J Gastroenterol* 99: 1523-1526, 2004. doi:10.1111/j.1572-0241.2004.30472.x.
- [15] Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 367: 1066-1074, 2006. doi:10.1016/S0140-6736(06)68397-9
- [16] King A, Allan DSJ, Bowen M, Powis SJ, Joseph S, Verma S, Hiby SE, McMichael AJ, Loke YW, Braud VM. HLA-E is expressed on trophoblast and interacts with CD94/NKG2 receptors on decidual NK cells. *Eur J Immunol* 30: 1623-1631, 2000. doi:10.1002/1521-4141(200006)30:6<1623::AID-IMMU1623>3.0.CO;2-M
- [17] King A, Boocock C, Sharkey AM, Gardner L, Beretta A, Siccardi AG, Loke YW. Evidence for the expression of HLA-C class I mRNA and protein by human first trimester trophoblast. *J Immunol* 156: 2068-2076, 1996.
- [18] Larsen MH, Hylenius S, Andersen AMN, Hviid TVF. The 3'-untranslated region of the HLA-G gene in relation to pre-eclampsia: revisited. *Tissue Antigens* 75: 253-261, 2010. doi:10.1111/j.1399-0039.2009.01435.x.
- [19] Le Bouteiller P, Pizzato N, Barakonyi A, Solier C. HLA-G, preeclampsia, immunity and vascular events. *J Reprod Immunol* 59: 219-234, 2003. doi:10.1016/S0165-0378(03)00049-4.
- [20] Misra DP. The effect of the pregnancy-induced hypertension on fetal growth: a review of the literature. *Paediatr Perinat Epidemiol* 10: 244-263, 1996. doi:10.1111/j.1365-3016.1996.tb00048.x.
- [21] Ni H, Yu XJ, Liu HJ, Lei W, Rengaraj D, Li XJ, Yang ZM. Progesterone regulation of glutathione S-transferase Mu2 expression in mouse uterine luminal epithelium during preimplantation period. *Fertil Steril* 91, Suppl: 2123-2130, 2009. doi:10.1016/j.fertnstert.2008.04.053.
- [22] Pawitan Y, Michiels S, Koscielny S, Gusnanto A, Ploner A. False discovery rate, sensitivity and sample size for microarray studies. *Bioinformatics* 21: 3017-3024, 2005. doi:10.1093/bioinformatics/bti448
- [23] Pröll J, Blaschitz A, Hutter H, Dohr G. First trimester human endovascular trophoblast cells express both HLA-C and HLA-G. *Am J Reprod Immunol* 42: 30-36, 1999. doi:10.1111/j.1600-0897.1999.tb00462.x.
- [24] Rajakumar A, Chu T, Handley DE, Bunce KD, Burke B, Hubel CA, Jeyabalan A, Peters DG. Maternal gene expression profiling during pregnancy and preeclampsia in human peripheral blood mononuclear cells. *Placenta* 32: 70-78, 2011. doi:10.1016/j.placenta.2010.10.004.
- [25] Sacks GP, Studena K, Sargent K, Redman CWG. Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *Am J Obstet Gynecol* 179: 80-86, 1998. doi:10.1016/S0002-9378(98)70254-6.
- [26] Shiina T, Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. *Tissue Antigens* 64: 631-649, 2004. doi:10.1111/j.1399-0039.2004.00327.x.
- [27] Shin S, Yoon JH, Lee HR, Hwang SM, Roh EY. Association of HLA-A, -B and -DRB1 genotype with birthweight and CD34 cell content: analysis of Korean newborns and their cord blood. *Mol Hum Reprod* 16: 338-346, 2010. doi:10.1093/molehr/gaq011.

- [28] Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 376: 631-644, 2010. doi:10.1016/S0140-6736(10)60279-6.
- [29] Sun CJ, Zhang L, Zhang WY. Gene expression profiling of maternal blood in early onset severe preeclampsia: identification of novel biomarkers. *J Perinat Med* 37: 609-616, 2009. doi:10.1515/JPM.2009.103.
- [30] Takakuwa K, Adachi H, Hataya I, Ishii K, Tamura M, Tanaka K. Molecular genetic studies of HLA-DRB1 alleles in patients with unexplained recurrent abortion in the Japanese population. *Hum Reprod* 18: 728-733, 2003. doi:10.1093/humrep/deg188.
- [31] Textoris J, Ivorra D, Ben Amara A, Sabatier F, Ménard JP, Heckenroth H, Bretelle F, Mege JL. Evaluation of current and new biomarkers in severe preeclampsia: a microarray approach reveals the VSIG4 gene as a potential blood biomarker. *PLoS One* 8: e82638, 2013. doi:10.1371/journal.pone.0082638.
- [32] Timsit YE, Negishi M. CAR and PXR: the xenobiotic-sensing receptors. *Steroids* 72: 231-246, 2007. doi:10.1016/j.steroids.2006.12.006.
- [33] Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 4: 97-104, 2014. doi:10.1016/j.preghy.2014.02.001.
- [34] Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* 52: 873-880, 2008. doi:10.1161/HYPERTENSIONAHA.108.117358