Title

"Current model systems for the study of preeclampsia"

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Table 3. Preeclampsia *in silico* research model systems

Models	Method	Species	Description	Advantages	Disadvantages	References
Gene prioritization	- Co-expression network construction. - Modular and node analysis. - Genetic algorithms applied in combination with the nearest neighbor and discriminant analysis classification methods.	Human	The gene prioritization in PE was explored, combining co-expression network analysis and genetic algorithm optimization approaches.	- It can integrate and analyze a large amount of information derived from 'omic' experimental approaches. - Co-expression network analysis combining both modular and gene-centered approaches are capable of identifying genes significantly related to PE.	- Nodes located in small subnetworks may report relatively high closeness centrality values. - The analysis of more samples than variables (genes) are recommended to avoid false discoveries (false relevant correlations).	(1)
Protein-protein interaction network analysis	- Several indexes of centrality were explored for hub detection as well as enrichment statistical analysis of metabolic pathways and disease.	Human	A comprehensive genes/proteins data set was created by the analysis of both public proteomic data and text mining of public scientific literature.	- This methodology leads to the identification of unknown interactions of proteins/genes and a better integration of metabolic pathways and PE.	- Experimental validation for new candidates is needed. - It is necessary to reduce the gene space applying other methodologies as well as to design new experimental experiences. - The limitation of the human protein interaction information suggests that orthologous genes should also be needed in order to increase the protein-protein interaction network, covering the initial data set, and to increase the capabilities of the metabolic	(2)

					pathways and disease enrichment analysis.	
Genetics of PE	Cluster analysis was used to aggregate extracted genes from the published literature into gene sets associated with PE. Gene ontology was used to organize this large group of genes into ontology groups.	Human	To identify candidate genes and genetic variants for PE, a bioinformatic approach was used to extract and organize genes and variants from the published literature.	- The gene sets presented are useful for: 1. Analyzing available data on PE. 2. Analyzing the genetic architecture of PE. 3. Clustering of genes associated with PE by phenotype and by source.	- The authors found a notable lack of consistency in the definition of PE in the literature. - Specific, well-defined phenotypes may be critical to understanding the genetic architecture of PE, and in the statistical power of data sets.	(3, 4)
Artificial Neural Networks	Artificial neural networks and multivariate logistic regression were applied to a set of clinical and laboratory data collected at different weeks of gestation. - The performance of each model was assessed using receiver operator characteristic (ROC) curves.	Human	- Model construction for: 1. Classification of women with normal blood pressure, high blood pressure and PE in different gestational ages using maternal heart rate variability indexes. 2. Predicting the development of PE in consecutive normotensive pregnant women at high risk of PE and intrauterine fetal growth retardation.	- ANN models: 1. Require less formal statistical training to develop. 2. Can detect complex nonlinear relationships between independent and dependent variables. 3. Have the ability to detect all possible interactions between predictor variables. 4. Can be developed using multiple different training algorithms. 5. Has the ability to learn how to do	- ANN models: 1. Has limited ability to identify possible causal relationships. 2. Requires greater computational resources. 3. Are prone to overfitting. 4. Development is empirical, and many methodological issues remain to be resolved.	(5, 6)

				tasks based on the data given for training or initial experience. 6. Can create its own organization of the information it receives during learning time. 7. ANN computations may be carried out in parallel. 8. Partial destruction of a network leads to the corresponding degradation of performance.		
Multivariate logistic regression model	A multivariate logistic regression model was used to evaluate the potential of biological markers, standard laboratory parameters, and biochemical and clinical factors to predict the occurrence of PE.	Human	Investigate the usefulness of several biological markers, clinical and standard laboratory parameters for the individual prediction of PE, after 10th week of gestation.	- Logistic regression: 1. Is more robust. The independent variables don't have to be normally distributed, or have equal variance in each group. 2. Does not assume a linear relationship between the variables. 3. Can add explicit interaction and power terms. 4. Distributed error terms are not assumed.	- Logistic regression: 1. Requires formal statistical training to develop. 2. Requires much more data to achieve stable, meaningful results. For logistic regression, at least 50 data points per predictor are necessary to achieve stable results. 3. If wrong independent variables are included, the model will have little to no predictive value. 4. Cannot predict continuous outcomes. 5. Requires each data point to be independent of all other data points.	(7-14)

					6. Is vulnerable to overconfidence.	

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