

An integrative system biology approach for dissecting Autism Spectrum Disorder

Asif M^{1,2}, Rasga C^{1,2}, Martiniano H^{1,2,3}, Santos JX^{1,2}, Marques AR^{1,2}, Couto FM³ and Vicente AM^{1,2,4}

¹Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa; ²BioISI - Biosystems & Integrative Sciences Institute, Lisboa; ³Departamento de Informática, Faculdade de Ciências, Universidade de Lisboa, Portugal;

⁴Instituto Gulbenkian de Ciência, Oeiras

Autism Spectrum Disorder (ASD) is characterized by a wide spectrum of behavioral presentation. Many genetic factors are implicated in ASD, however their role in the heterogeneous ASD phenotype remains elusive. Using data mining-based integrative approaches, we seek to identify patterns of association between ASD phenotypic subgroups and altered biological processes inferred from CNVs targeting brain genes.

Analysis of ASD clinical data from 2067 patients, using Agglomerative Hierarchical Clustering, identified three distinct phenotypic clusters. These clusters differed in overall adaptive behaviour profiles (assessed by Vineland Adaptive Behavior Scales) and verbal status (assessed by Autism Diagnostic Interview-Revised). In Cluster 1, 72% of the individuals presented dysfunctional patterns of adaptive behavior, while all were verbal; Cluster 2 represented the subgroup with the most severe clinical presentation, with all patients non-verbal and 87% showing dysfunctional adaptive behaviour profiles; All patients in cluster 3 were verbal and only 56% of individuals exhibited dysfunctional adaptive behaviour, indicating a less severe phenotype.

In the same ASD subjects, analysis of rare CNVs targeting brain genes, using enrichment methods, predicted 21 statistically significant biological processes; several of these, like neuron-neuron synaptic transmission and nervous system development, are consistent with reported literature for ASD.

We are currently performing data mining using Classification And Regression Trees (CART) to uncover associations between the identified phenotypic clusters and brain biological processes. Our final objective with this approach is to develop a novel integrative method, allowing the prediction of clinical outcome from biological processes defined by genetic alterations, while further understanding ASD disease mechanism.

This study was funded by Fundação para a Ciência e Tecnologia (FCT).