

1) AUTISM SPECTRUM DISORDER (ASD)

Is a neurodevelopmental disorder characterized by **communication deficits and restricted, repetitive patterns of behavior** [1], with heterogeneous clinical presentation, variable severity, and multiple comorbidities. A complex underlying genetic architecture matches the clinical heterogeneity, and evidence indicates that **several co-occurring brain disorders share a genetic component with ASD**.

2) OBJECTIVES

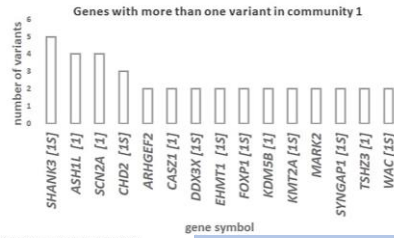
- To **infer the genetic similarity between ASD and other brain disorders co-occurring with ASD**, including disease subtypes, using **disease similarity network analysis**;
- To identify the **communities of diseases that have higher genetic similarity with ASD**, applying the **Leiden algorithm**;
- To **identify likely pathogenic mutations in a large ASD sequencing dataset** that may explain the genetic similarities conferred by rare variants across ASD and comorbid brain disorders.

4) RESULTS & DISCUSSION

•We identified **3 communities of diseases** (Fig.1). **Community 1** is genetically more similar to ASD and includes **Epilepsy, Bipolar Disorder (BP), Attention-Deficit/Hyperactivity Disorder (ADHD) combined type, and some disorders in the Schizophrenia Spectrum (SCZ)**. Most of the disorders of Community 2 are **SCZ subtypes, and Intellectual Disability (ID) is highly represented in Community 3**

•**ID and ASD are in separate communities**. The results show that there is enough genetic distance to place both disorders in separate communities. **Community 1 is enriched in signal transduction and neuronal system mechanisms**, which have been implicated in some diseases from this community, as the dysfunction in neuronal apoptosis-regulatory pathways in Epilepsy, or alterations in G-protein coupled receptors in ASD, Schizophrenia and Bipolar Disorder;

•The genes **SHANK3, ASH1L, SCN2A and CHD2**, which have a higher number of **de novo rare loss of function (LoF) Single Nucleotide Variants in ASD subjects**, are **candidate genes for diseases in all three communities**. These genes are strong candidates for ASD.



4) DISEASE SIMILARITY NETWORK AND COMMUNITIES

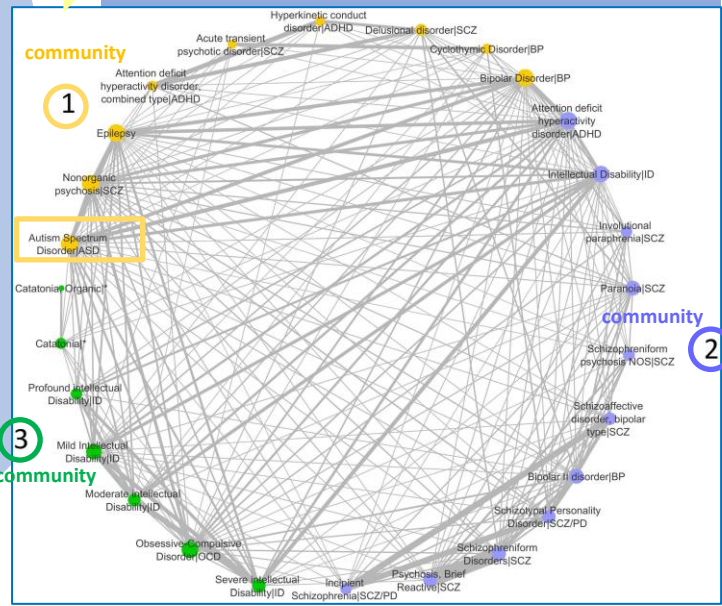
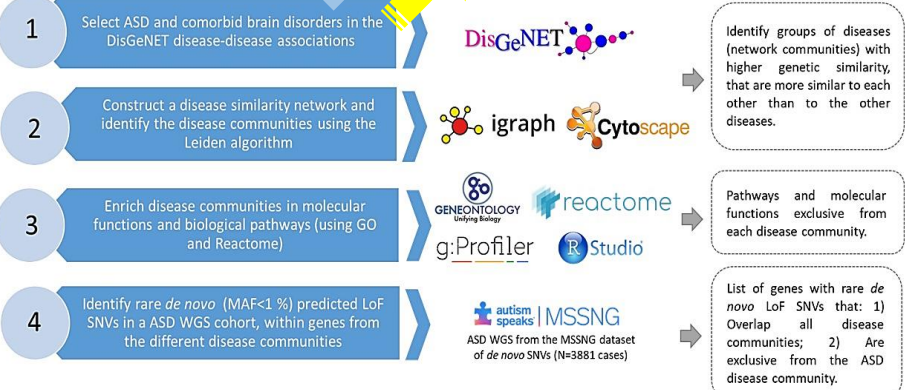


Fig 1. Disease similarity network. The different communities are indicated with nodes of different colors in the network, and the diseases included in each community are shown in the figure. Community 1 disorders nodes are presented in yellow.

3) WORKFLOW



5) CONCLUSIONS

This work provided further **evidence for a shared genetic architecture between ASD and several other brain disorders, including some frequent comorbidities of ASD**. It also identified genes and biological processes that overlap between brain disease communities and showed that **ASD patients present rare *de novo* LoF variants in genes previously associated with frequent comorbid disorders**.

References:[1] DSM-5 American Psych. Assoc. (2013). Diagnostic and statistical manual of mental disorders. Arlington: Amer. Psych. Pub. Acknowledgements: Joana Vilela is recipient of a fellowship from BioSys PhD programme (Ref: PD/BD/131390/2017 from FCT (Portugal)). We wish to acknowledge the resources of MSSNG (www.mss.ng), Autism Speaks, and The Centre for Applied Genomics at The Hospital for Sick Children, Toronto, Canada. We also thank the participating families. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.