

Evolutionary and Developmental Signatures of Cortical Folding: Genomic Human Accelerated Regions and Sulcal Pits Variation in Schizophrenia

Noemí HOSTALET^{1,2,3*}, Mateo BERRIO-SOTO^{1,4}, Daniel HERRERA-ESCARTÍN², Lluís COBOS-AUMATELL⁵, Maria GUARDIOLA-RIPOLL^{6,7}, Banu AHTAM^{8,9}, Ana AQUINO¹, Irene PARÍS-GÓMEZ¹, Amalia GUERRO-PEDRAZA¹⁰, Pedro CANUT¹⁰, Jesús J GOMAR¹¹, Pilar SALGADO-PINEDA^{1,3}, Josep SALAVERT¹², Núria RAMIRO¹², Emilio J INAREJOS CLEMENTE¹³, Salvador SARRÓ^{1,3}, Raymond SALVADOR^{1,3}, Kiho IM^{8,9}, Edith POMAROL-CLOTET^{1,3}, Mar FATJÓ-VILAS^{1,2,3}

¹FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain, ²Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals (BEECA), Facultat de Biologia, Universitat de Barcelona (UB), Spain.

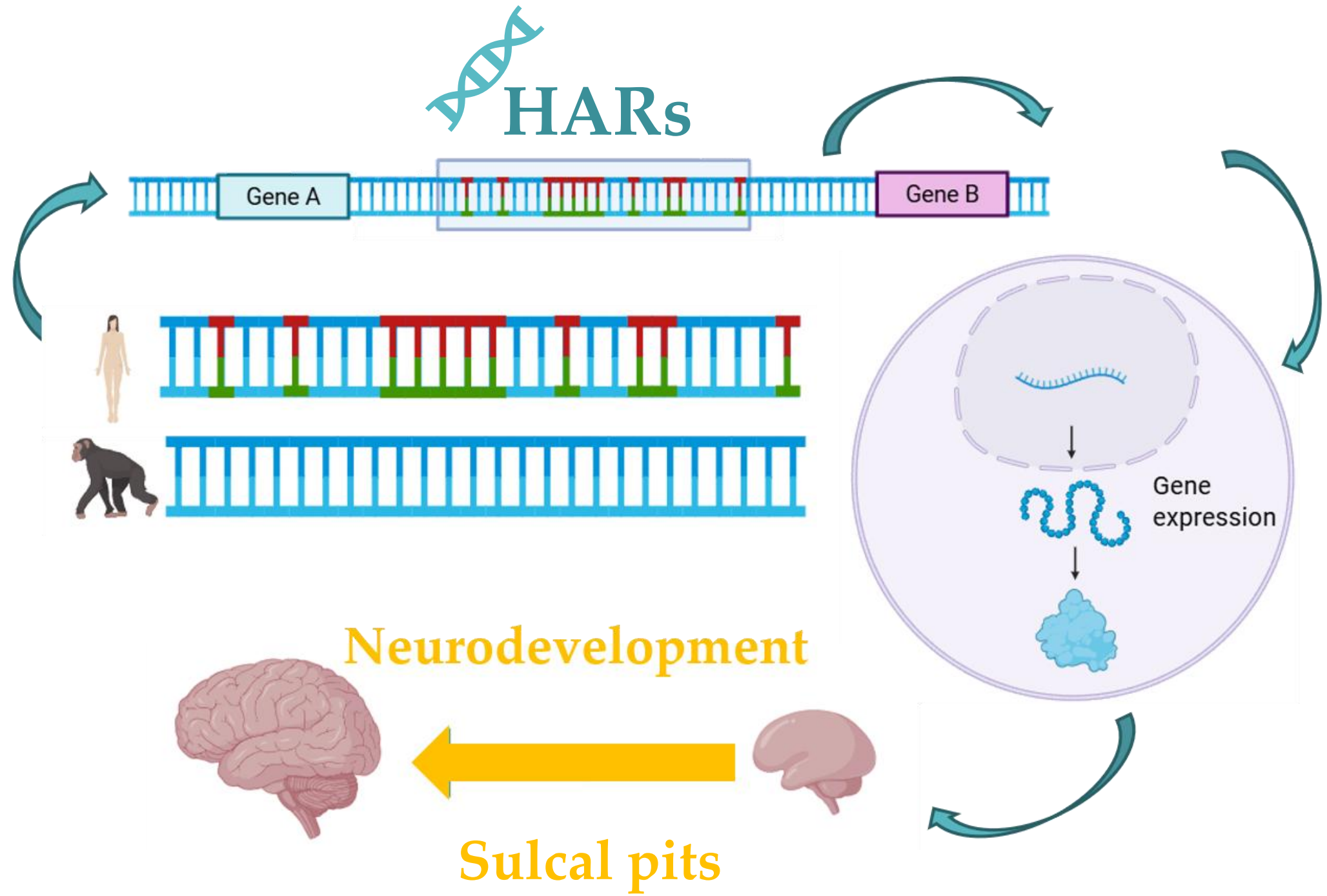
³Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Spain, ⁴Environment and Society Research Group (MASO) – Faculty of Social and Human Sciences, University of Antioquia, Colombia.

⁵Freelance computing assessor, Barcelona, Spain, ⁶Institut d'Investigació Sanitària Pere Virgili (IISPV-CERCA), Reus, Spain, ⁷Hospital Universitari Institut Pere Mata (HUIPM), Reus, Spain, ⁸Fetal Neonatal Neuroimaging and Developmental Science Center, Division of Newborn Medicine, Boston Children's Hospital, Boston, MA, USA, ⁹Department of Pediatrics, Harvard Medical School, Boston, MA, USA, ¹⁰Fundación Hospitalarias Sant Boi, Sant Boi de Llobregat, Barcelona, Spain.

¹¹The Litwin-Zucker Alzheimer's Research Center, The Feinstein Institutes for Medical Research, Manhasset, USA, ¹²Fundación Hospitalarias Barcelona, Barcelona, Spain, ¹³Servei de Radiologia, Hospital Sant Joan de Déu, Barcelona, Spain.

Introduction

- ✓ Human Accelerated Regions (HARs), rapidly evolved genomic elements, are thought to shape human-specific brain features by influencing early cortical development (1).
- ✓ Sulcal pits, the earliest and most stable folding features of the cerebral cortex, provide an adult-accessible window into prenatal brain development (2).
- ✓ Disruptions in these mechanisms may underlie atypical folding patterns in schizophrenia, a disorder often viewed as a by-product of evolutionary adaptations supporting human cognition



Objectives

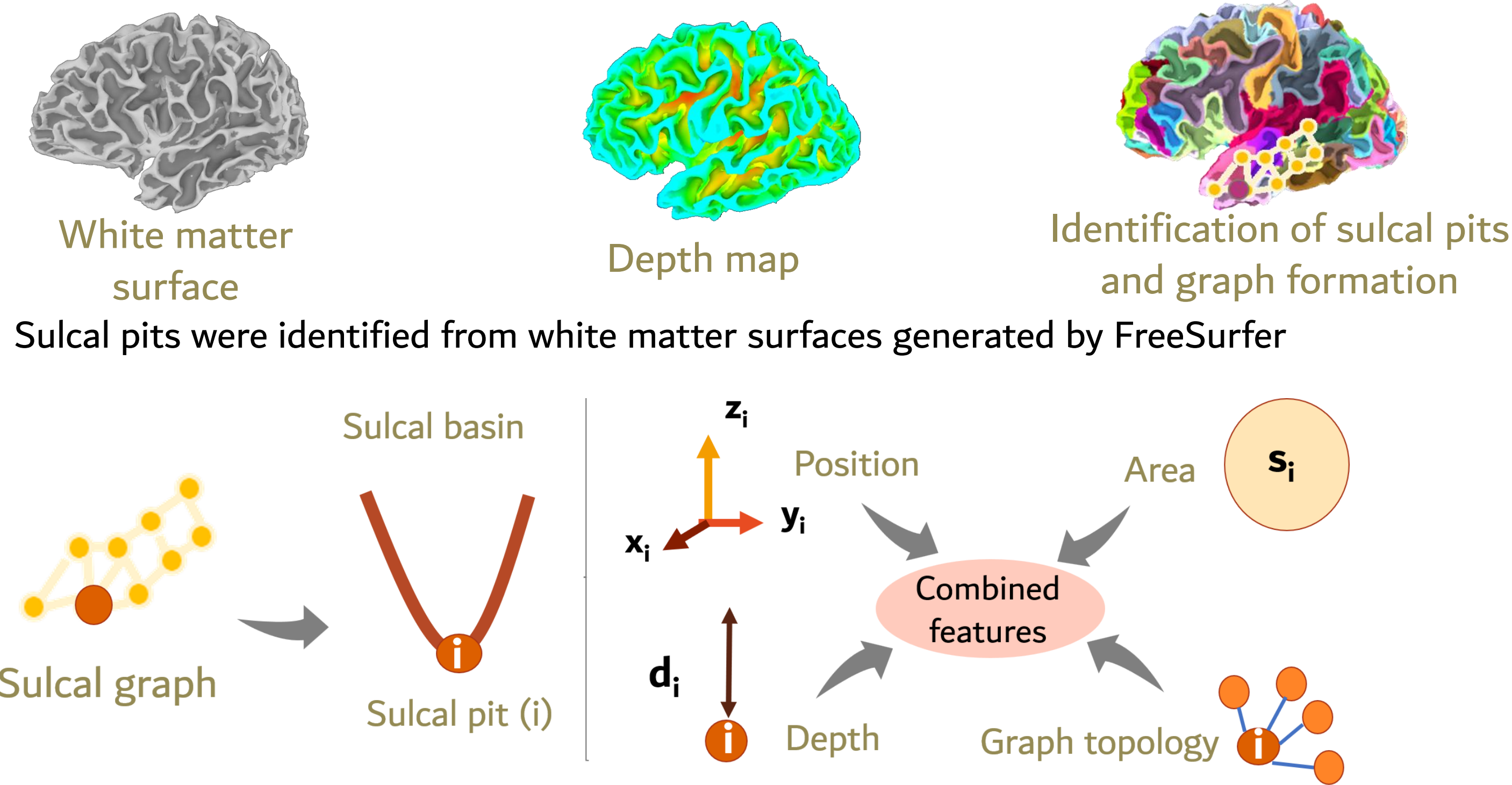
- 1 To characterize divergence in sulcal pit patterns between individuals with SZ and healthy controls
- 2 To assess whether prenatal HARs-related gene expression is associated with this variation.

Methods

Sample: 189 healthy controls (HC) and 237 patients with schizophrenia (SZ)

1 Divergence analysis of sulcal pits patterns

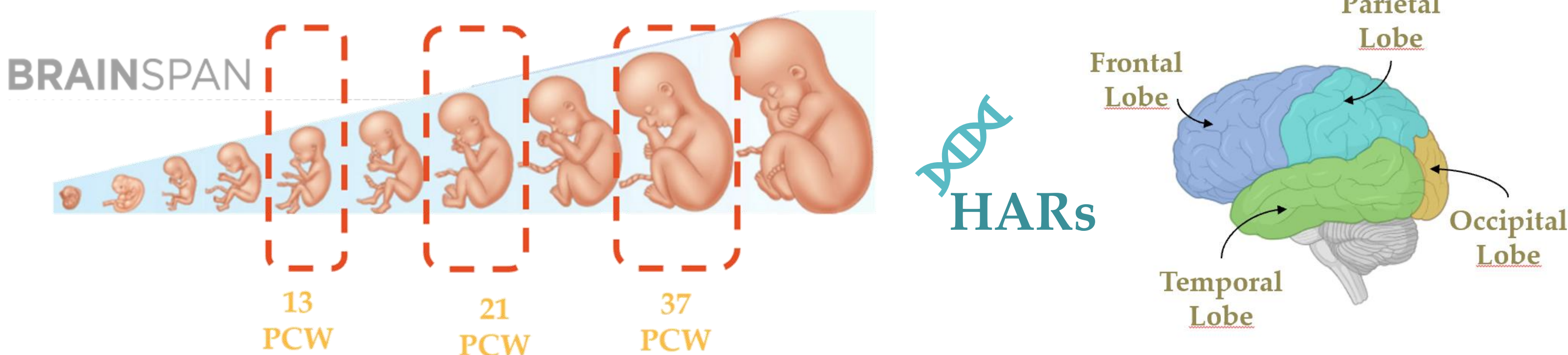
Sulcal pits extraction



Graphs were created for each hemisphere and lobe, treating sulcal pits as nodes and their connections as edges, and were compared between HC and SZ patients based on 5 measures: area, depth, position, graph topology and all combined features (3).

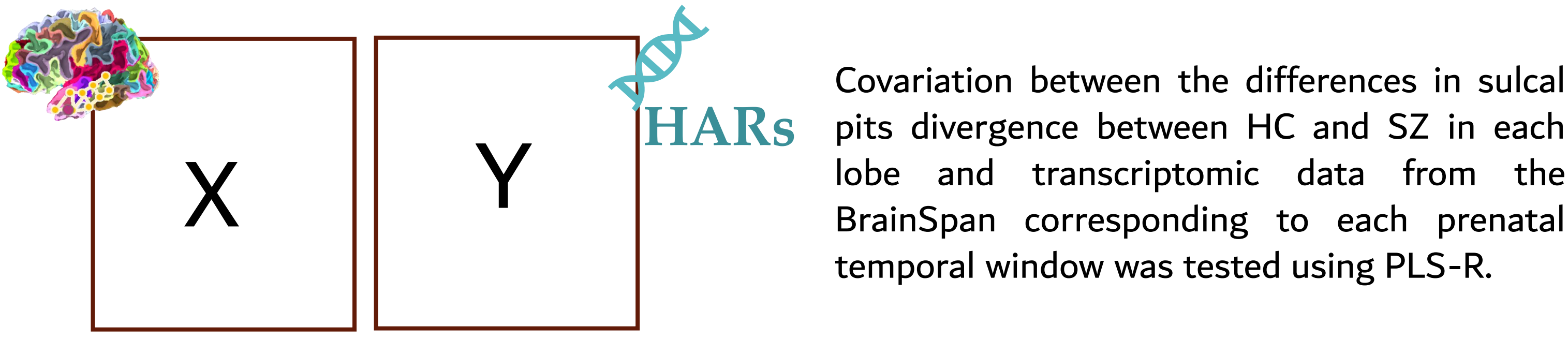
2 Association between prenatal HARs genes and sulcal pits variation

HARs transcriptomic data from the BrainSpan averaged by lobe



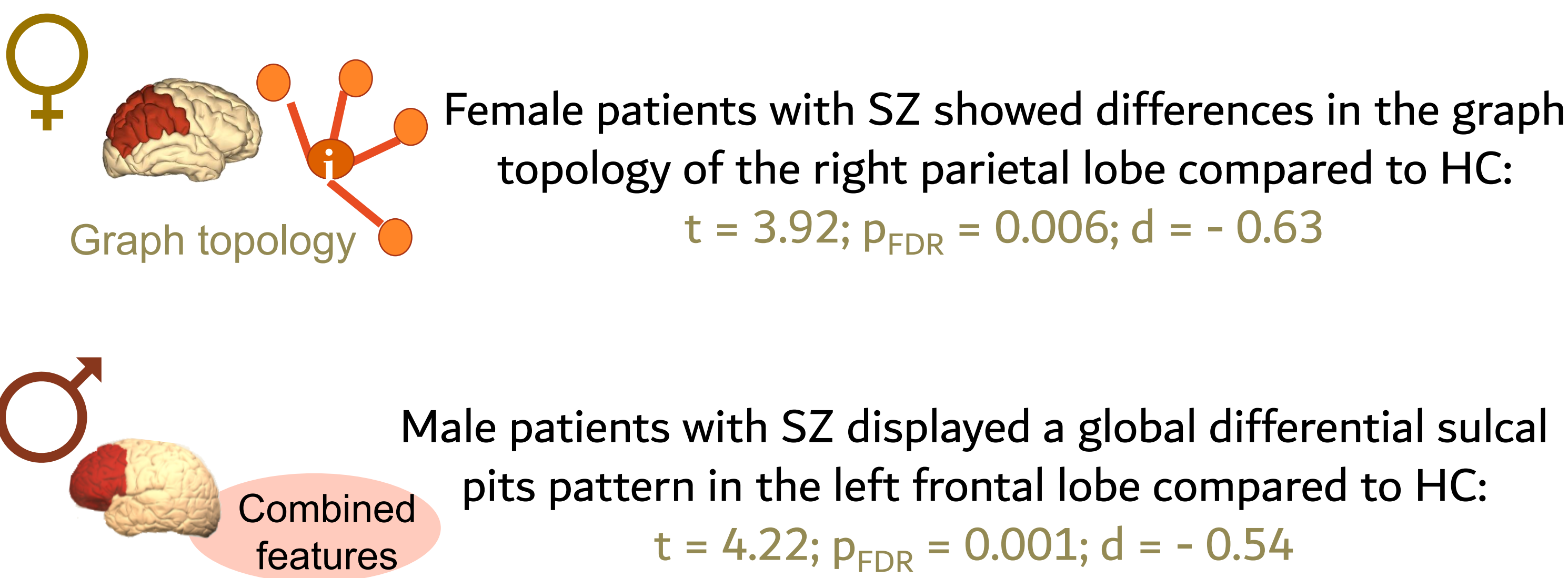
Selection of 179 HARs-related genes from the BrainSpan database and averaging of their expression by lobe across three prenatal developmental windows.

Partial Least Squares Regression Analyses (PLS-R)



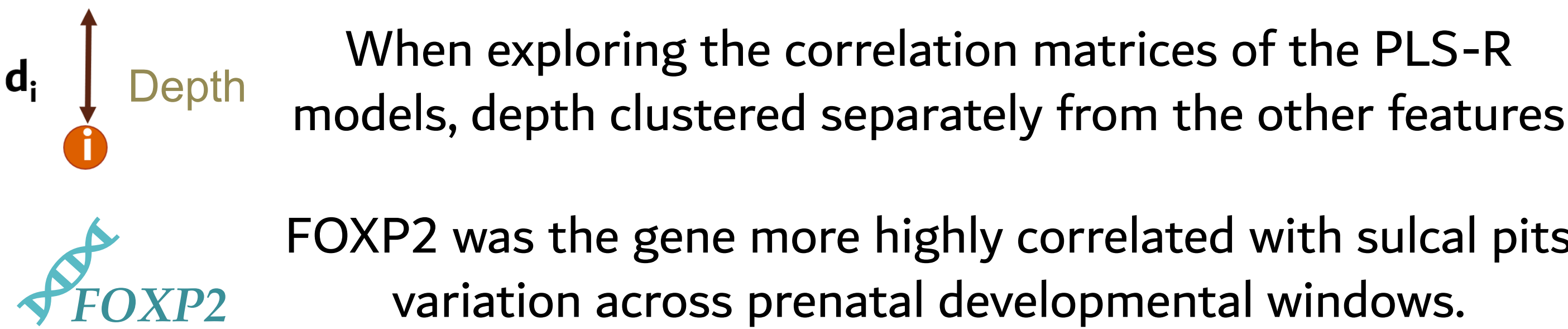
Results

1 Divergence analysis of sulcal pits patterns



2 Association between prenatal HARs genes and sulcal pits variation

The first component of the PLS-R across temporal windows explained 52 – 61% of sulcal pits differences



The performance of the PLS-R indicated that we should consider the results exploratory ($Q^2 < 0$)

Conclusions

- 1 We identified sex-specific patterns of sulcal pits in patients with schizophrenia in the left frontal lobe, a region related to cognitive human-specific abilities

- 2 FOXP2 expression was associated with differences in sulcal pits depth. This gene has been related with evolutionary aspects of language in humans and with specific schizophrenia phenotypes

References

1) Guardiola et al. Int J Mol Sci. 2023 Feb 10;24(4):3597.doi: 10.3390/ijms24043597; 2) Hostalet et al. Prog Neuropsychopharmacol Biol Psychiatry. 2025 Mar 20;137:111289.doi: 10.1016/j.pnpbp.2025.111289; 3) Im, K., et al. Neuroimage. 2019 Jan 15;185:881-890.doi: 10.1016/j.neuroimage.2018.03.057