Abnormal Sulcal Pattern in Children with 16p11.2 Deletion and Duplication Syndrome

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Introduction

The 16p11.2 chromosome is a susceptible region to a recurrent ~600 kb BP4-BP5 copy number variant [1,2].

16p deletion and duplication syndromes are well characterized as genetic causes for Autism Spectrum Disorder and other neurodevelopmental disorders, [3,4] and present with opposing phenotypes among patients in measurements such as body mass index and brain volume [5].

This study aims to evaluate sulcal patterns in pediatric patients presenting with 16p deletion and duplication syndrome.

The primary sulcal folding patterns develop in-utero and are genetically determined with little changes after birth [6].

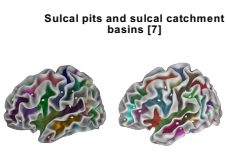
Therefore, the analysis of sulcal patterns could characterize the impact of CNV over 16p11.2 chromosome, leading to improved characterization of brain development in this cohort.

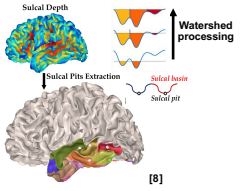
Methods

Participants:
Data from 39 pediatric-deletion (M=11.1y, SD=3.1y, 19 females) and 12 pediatric-duplication (M=10.6y, SD=3.3y, 5 females) patients were compared with 21 age-matched controls (M=12.7y, SD=2.3y, 7 females).

MRI Acquisition:
MRI imaging was performed at two different sites (University of California Berkeley and Children's Hospital of Philadelphia) using 3T scanners with a 32-channel head coil each. This data is part of the advanced neuroimaging protocol of the Simons VIP project [1].
Imaging protocol included an axial 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) T1-weighted sequence (TE=1.64ms; TR=2530ms; TI=1200ms; flip angle=7°, FOV=256mm)

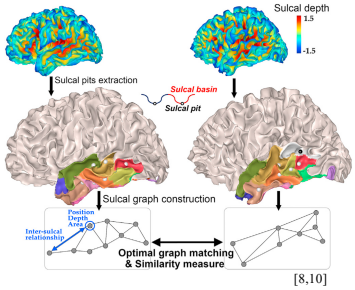
Image Processing:
Freesurfer was used to process the T1-weighted images and to extract cortical surfaces. Sulcal pattern is represented with a graph structure using sulcal pits as the nodes. Sulcal pits are the deepest local regions of sulci, closely related to functional areas under strict genetic control [6,7]. A watershed algorithm, based on sulcal depth map, was used to identify sulcal pits and their corresponding sulcal catchment basins on the white matter surface. If sulcal basins met, sulcal pits in the basins were connected with an edge.





For sulcal geometry, we used 3D position (x,y,z) and depth of sulcal pit, and area of sulcal basin. To reflect sulcal arrangement and patterning, we used graph topology, defined as the number of connections with 1st neighborhood nodes (the number of edges) on each node and the paths between nodes in the graph. We adapted a spectral matching technique to determine the optimal match between different sulcal graphs and compute the similarity value (0~1) [9].

Using the graph-based sulcal pattern comparison method, sulcal pattern similarities of all possible pairs in two groups were computed for both hemispheres and frontal, temporal, parietal, and occipital lobar regions. After measuring similarity with all combined features (sulcal position, area, depth, graph topology), we measured similarity using each individual feature by setting all weights of the other features to 0 to evaluate their relative importance on the sulcal pattern similarity. We statistically tested if similarity between 16p-del and TD, and 16p-deletion and TD was significantly different when compared to similarity within TD group.



Results

16p groups showed significantly low similarity to TD in both hemisphere for combined features ($p<0.05$). Significantly lower mean similarity between 16p-deletion and TD were observed for position and depth in both hemispheres, and area and graph topology in left. Significantly lower mean similarity between 16p-duplication and TD were observed for position and depth in left and position in right hemisphere. All significance levels remained after FDR correction.

	TD	16p-del	P value	16p-dup	P value
L Hemisphere	0.7614 (0.0045)	0.7493 (0.0099)	<0.0001*	0.7524 (0.0056)	<0.0001*
L Frontal	0.7675 (0.0049)	0.759 (0.0085)	0.0001*	0.7639 (0.0081)	0.1324
L Temporal	0.7564 (0.0100)	0.7468 (0.0133)	0.0061*	0.7469 (0.0119)	0.0236
L Parietal	0.7429 (0.0085)	0.7316 (0.0152)	0.0031*	0.7295 (0.0089)	0.0002*
L Occipital	0.7483 (0.0199)	0.7456 (0.0137)	0.5505	0.7550 (0.0074)	0.2803
R Hemisphere	0.7588 (0.0046)	0.7486 (0.0098)	<0.0001*	0.7521 (0.0063)	0.0018*
R Frontal	0.7694 (0.0065)	0.759 (0.0104)	0.0001*	0.7665 (0.0058)	0.2200
R Temporal	0.7659 (0.0122)	0.7528 (0.0159)	0.0020*	0.7532 (0.0118)	0.0086*
R Parietal	0.7291 (0.0106)	0.7245 (0.0118)	0.1471	0.7243 (0.0106)	0.2394
R Occipital	0.7529 (0.0172)	0.7427 (0.0153)	0.0243*	0.7522 (0.0131)	0.9012

Conclusions

Our results provide further evidence of sulcal pattern abnormalities in pediatric patients with 16p-deletion and duplication. These findings direct future investigation about the impact of CNV within the 16p11.2 chromosome and the impacts on childhood brain development.

References

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