

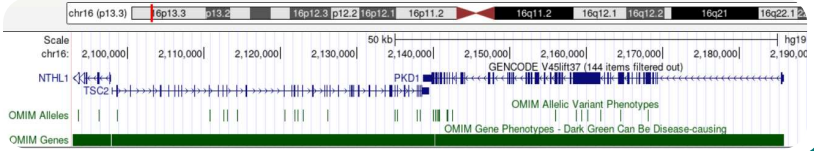
Atypical noncontiguous TSC2/PKD1 gene deletions presenting as tuberous sclerosis/polycystic kidney disease contiguous gene syndrome

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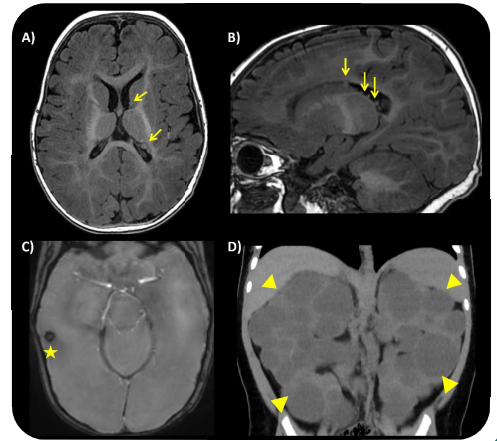
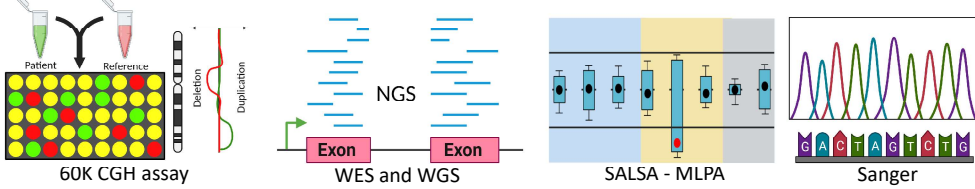
BACKGROUND

Tuberous sclerosis complex (TSC) and autosomal dominant polycystic kidney disease (ADPKD) are genetically distinct disorders typically associated with pathogenic variants in *TSC1* and *TSC2* for the former and *PKD1* and *PKD2* for the latter. *TSC2* and *PKD1* lie adjacent to each other, and large deletions comprising both genes lead to *TSC2/PKD1* contiguous gene deletion syndrome (CGS), with a distinctive phenotype of early onset. All described cases of *TSC2/PKD1* CGS are caused by large deletions that disrupt both genes. No known cases of two independent deletions have been described in this syndrome.



CASE PRESENTATION AND METHODS

A 16-month-old girl, second child of healthy non-consanguineous parents, was initially evaluated in the neonatal period due to cystic kidney disease. Her course was complicated with several TSC associated manifestations before the first year of age (West syndrome, Wolff-Parkinson-White syndrome, subependymal nodules and cortical tubers on brain MRI). All these findings suggested a likely diagnosis of *TSC2/PKD1* CGS and molecular and genetic investigations to confirm the diagnosis were undertaken.



Objective: To identify genetic abnormalities that could potentially cause all the manifestations on the girl. We also aim to establish whether it was a *de novo* or an inherited disorder.

RESULTS

Normal karyotype and 60K CGH assay
Absence of significant gains or losses of genetic material

WES

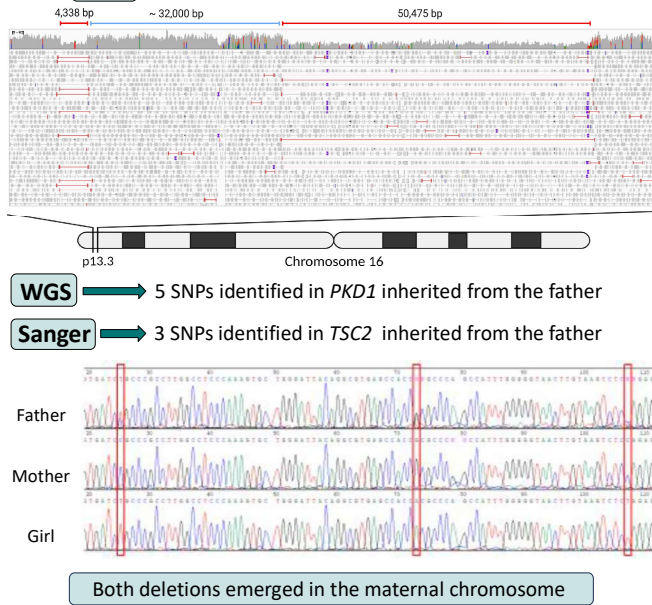
VUS
PKD1 → c.5245G>A
p.V1749I (maternally inherited)
TSC2 → c.4166C>G
p.P1389R (de novo in exon 31)

CNVs
Suspected 2 *de novo* non-contiguous partial gene deletions in *PKD1* and *TSC2*

MLPA

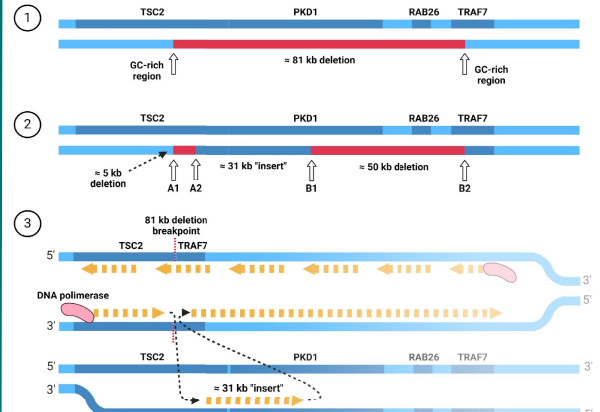
TSC2 deletion (exons 27-32)
PKD1 deletion (5' UTR - exon 7)

WGS Heterozygous deletions in *TSC2* and *PKD1*



Implicated gene	Deletion breakpoints	Location (genome)	Sequence
<i>TSC2</i>	Chr16: 2,128,351	Chr16: 2,128,430	5' CTGGCCAG 3'
	Chr16: 2,132,688	Chr16: 2,132,668	
<i>TSC2</i>	Chr16: 2,128,351	Chr16: 2,128,348	5' GGAAGCCC 3'
	Chr16: 2,132,688	Chr16: 2,132,835	
<i>PKD1</i>	Chr16: 2,164,518	Chr16: 2,164,450	5' CGTGGCC 3'
	Chr16: 2,214,992	Chr16: 2,215,000*	

Proposed mechanism: FoSTeS (Fork Stalling and Template Switching)



CONCLUSIONS

This study presents a unique case of *TSC2/PKD1* CGS caused by two *de novo*, noncontiguous partial deletions in the *TSC2* and *PKD1* genes, likely arising from the maternal germline. Parental WES and patient's WGS did not reveal any mosaicism or complex genomic rearrangements, suggesting that both deletions occurred independently although the probability is very scarce. Based on some evidence based on homology regions at the breakpoints, we speculate that the deletions could result from a FoSTeS mechanism. In conclusion, this is the first time to describe the *TSC2/PKD1* CGS caused by two partial deletions with a deleterious effect on the proteins, leading to the complete clinical manifestations associated with the syndrome.

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