CASE REPORT

Pitt–Hopkins syndrome (PTHS)– a case report from Pakistan

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Abstract

Pitt–Hopkins syndrome (PTHS) is a rare genetic neurodevelopment disorder where affected individuals exhibit symptoms such as severe developmental delays and intellectual disability. To the best of our knowledge, this report presents the first known case from Pakistan where Chromosomal Microarray Analysis (CMA) was employed to diagnose PTHS. The CMA revealed a deletion in the Transcription Factor 4 (TCF4) gene, confirming the diagnosis. This case underscores the clinical features, diagnostic process, and the significance of CMA in diagnosing rare genetic disorders such as PTHS, particularly in resource-limited settings.

Keywords: Pitt–Hopkins syndrome, TCF4 gene, Chromosomal Microarray Analysis, Pakistan case report.

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Introduction

PTHS is an autosomal dominant condition caused by mutation in the TCF4 gene on chromosome region 18q21.2.[1] Estimates indicate that PTHS affects about 1 in 200,000 to 300,000 individuals globally.[2] It can be diagnosed by detecting variations in the TCF4 gene, with about 40% of cases involving point mutations, 30% small deletions or insertions, and another 30% large deletions.[3] Most cases of PTHS are caused by de novo deletions and therefore are not inherited.[4] To the best of our knowledge, this is the first report of PTHS from Pakistan and describes the value of utilising CMA as part of diagnostic workup when a phenotype may be indistinguishable from many other inherited disorders.

Case Report

A 5-month-old female patient was first evaluated on 4 January 2020 at the Genetics Clinic, Aga Khan University Hospital, Karachi, Pakistan. She was born at 36 weeks of gestation via Lower Segment Caesarean Section (LSCS), with a birth weight of 2.4 kg. The neonatal period was notable for poor latching and sucking difficulties. She was the first child of non-consanguineous parents; her father was 40 years old and her mother 30 years old at the time of birth. A foetal anomaly scan conducted at 20 weeks of gestation was unremarkable, with no congenital anomalies detected.

At 5 months of age, the patient presented with frequent episodes of aspiration and the onset of seizures. However, a comprehensive workup was not initiated at that time—no Electroencephalogram (EEG) was performed, and anticonvulsant therapy was not commenced.

Over the following months, she demonstrated significant developmental delays, achieving neck holding at 9 months, but with absent grip, failure to reach for objects, and inability to roll over. A brain MRI was not available for this case.

On physical examination, she exhibited bitemporal narrowing, a broad nasal tip, thick lips, and a smooth philtrum. Reflexes were brisk, raising concerns of neurological involvement. By 11 months of age, she showed clear signs of global developmental delay, intellectual disability, and dysmorphic features. At this stage, she weighed 12.1 kg and measured 80 cm in height, indicating significant overweight for her age.

Given the clinical presentation, a genetic aetiology was strongly suspected. A comprehensive diagnostic workup, including CMA, was therefore initiated. The family history was unremarkable for genetic disorders (Figure 1).

CMA was performed on the proband's blood DNA using the Affymetrix CytoScan 750K array and scanned on GeneChip Scanner 3000 7G (Affymetrix, Santa Clara, CA USA). To detect copy number variations and assess their clinical significance the database of Genomic Variants (DGV, http://projects.tcag.ca/variation) was used. CMA analysis examined the whole human genome with high resolution. Deletions, duplications, loss of heterozygosity for all chromosomes was screened. CMA analysis of the proband revealed a pathogenic deletion on chromosome 18, spanning 14.8 Mb at arr[GRCh38] 18q21.2-22.1 x1 (Figure 2A). Log2 ratio analysis revealed it was a

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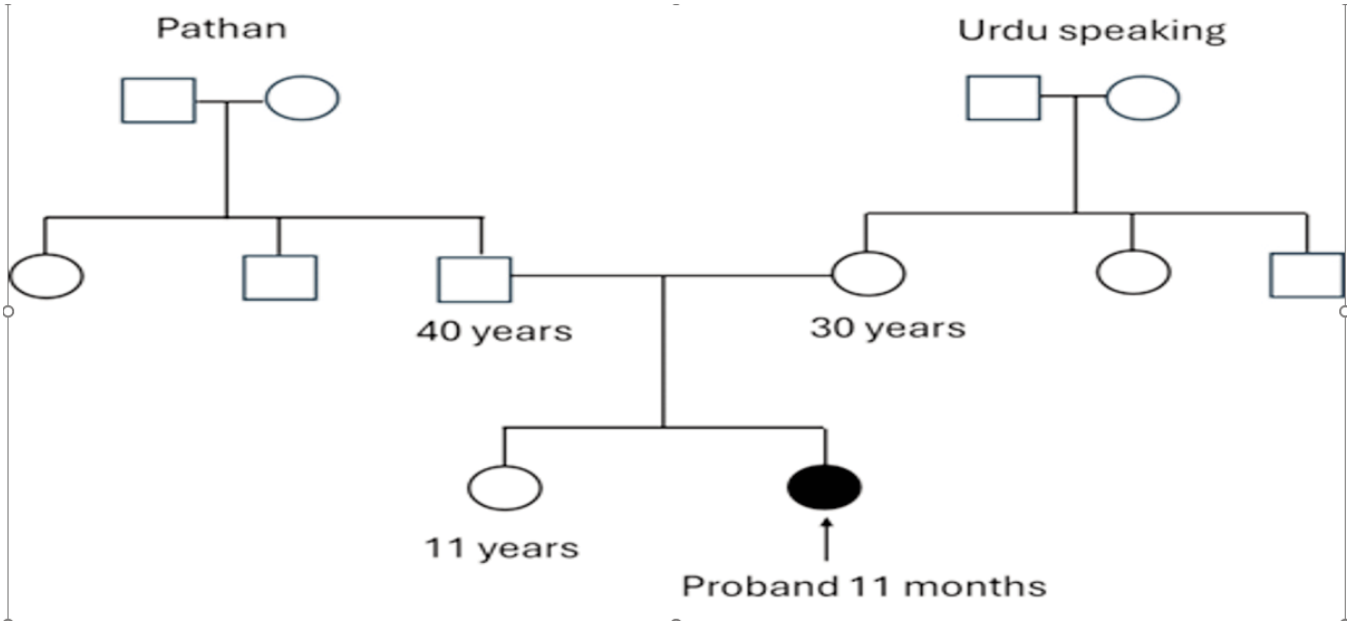

Figure-1: A pedigree of the family. Squares are males, circles are females. Filled in shapes are affected individuals. The arrow indicates the proband.

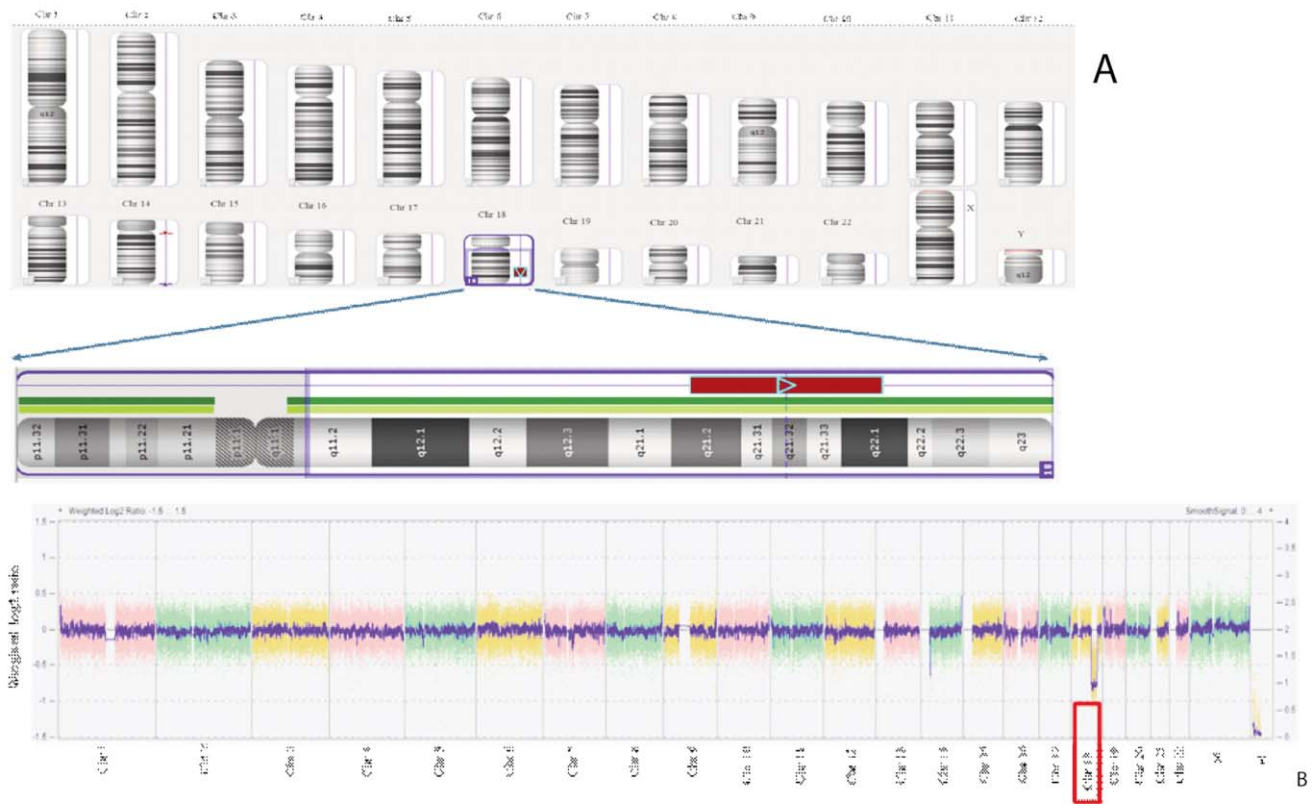

Figure-2: A deletion detected by CMA. (A) Affymetrix CytoScan 750k CMA analysis of chromosome 18 detects a 14.8 Mb deletion at arr[GRCh38] 18q21.2-22.1 (52251368_67097511) x1, including TCF4 gene. (B) The deletion (represented by a red bar) is indicative of decreased weighted log2 ratio and copy number state

heterozygous deletion with CNV state as x1 (Figure 2B). Additionally, haploinsufficiency of the TCF4 gene located at 18q21.2 region was identified by CMA.

Written informed consent for publication of this case report was obtained from both parents, as the patient is under 18 years of age. Ethical approval for this study was granted by the Ethics Review Committee of Aga Khan University (Approval No. 2024-10098-30838).

Discussion

This case describes the utility of CMA for detecting a 14.8 Mb deletion on chromosome 18 region 18q21.2-22.1 including haploinsufficiency of the TCF4 gene that allowed the diagnosis of a patient with PTHS. It underscores the complexity of diagnosing patients with neurological disorders in a setting where molecular genetic testing is limited and hard to access. Therefore, there was a diagnostic delay in identifying the genetic condition present.

At the Aga Khan University Clinical Laboratories, the Section of Molecular Pathology had the first service to offer CMA for constitutional genetic testing. It is useful for testing in cases where the clinical features are like those of various other genetic disorders. Our findings suggest that the dysmorphic features, developmental delay/intellectual disability are characteristic of PTHS and its association with TCF4 gene haploinsufficiency.[5,6] Like our observation, most cases of PTHS are caused by a de novo mutation and therefore there was no parental history of the condition. Cases of inheritance from a mosaic parent with a de novo mutation are exceedingly rare.[7]

Recent studies have further clarified the variable expressivity of TCF4 mutations[6] and highlighted epilepsy as a key phenotype in PTHS.[7] These findings emphasise the importance of early diagnosis, comprehensive clinical evaluation, and targetted genetic testing to improve patient care.

Affected individuals often go undiagnosed or misdiagnosed, making it difficult to determine the true frequency of the disorder in the general population. With the publication of an increasing number of cases, a better picture of associated symptoms and prognosis of individuals with PTHS will emerge. Prenatal diagnosis is possible for pregnancies at increased risk of PTHS, and parents can be counselled and further advised. This case underscores the importance of interdisciplinary collaboration in paediatric medicine and molecular genetics for the pursuit of accurate diagnoses to guide appropriate interventions and support for affected individuals and their families.

Conclusion

Reported is the first confirmed case of Pitt–Hopkins syndrome (PTHS) from Pakistan diagnosed using Chromosomal Microarray Analysis (CMA), highlighting the crucial role of advanced molecular diagnostics in identifying rare neurodevelopmental disorders. Early diagnosis allows timely clinical intervention, appropriate developmental support, and informed family counselling.

Recommendations: As PTHS is a genetic condition most often caused by a de novo mutation, recurrence risk for parents is generally low; however, genetic counselling is essential to explain inheritance patterns, discuss available testing options, and provide emotional and social support. Public awareness regarding rare genetic disorders is also important so that affected families seek specialist care earlier rather than attributing developmental delays to environmental or social factors. Strengthening access to genetic services, including CMA and counselling, will help improve long-term outcomes for children with rare genetic disorders and support informed reproductive decision-making for families.

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Conflict of Interest: None.

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AUTHORS' CONTRIBUTIONS:
AN, BA, SI, ZA & ZH: Concept, design, data acquisition, analysis, interpretation and final approval.