INTRODUCTION

There are more than 100 reports in the literature of terminal or interstitial deletions of 2q. The clinical manifestations vary according to the size of deletion and its location. Two relatively common small interstitial deletions have been reported: (a) deletion 2q21.1, characterized by mild intellectual disability, behavioral problems and a neurological disorder; and (a) deletion 2q22.1-q22.3, characterized by severe intellectual disability (Bravo-Oro et al., 2015; Gimelli et al., 2014; Greally, Robinson, Allen, O’Donovan, & Crolla, 2014; Mulatinho et al., 2012). A deletion involving 2q23.1 has been reported and this patient had short stature, learning and behavioral difficulty, autism and hyperactivity disorder (Mullegama et al., 2014; Noh & Graham, 2012; van Bon et al., 2010). Cases with interstitial deletion 2q31-q33 showed distinctive dysmorphic features, developmental delay and severe mental retardation. Compared with high-resolution chromosome banding by conventional karyotyping methodology, the exact breakpoints of deletions and duplications are delineated by Comparative Genomic Hybridization (aCGH). This has lead to the discovery of numerous microdeletion and microduplication syndromes (Ezugha et al., 2010; Lockwood, Chari, Chi, & Lam, 2006; Van Buggenhout et al., 2005).

In this presentation we describe a novel interstitial deletion encompassing 2q21.1–q23.3 which was diagnosed by aCGH. The deleted region includes 56 genes, 28 of which are reported in OMIM database with particular impact of haploinsufficiency of dose-sensitive genes is shown to contribute to the patient’s phenotype.
12 genes on broadening the phenotypic spectrum. Among those genes there were dose-sensitive genes that could manifest a phenotype when caused by haploinsufficiency, that is, ZEB2 (OMIM 605802), MBDS (OMIM 611472), and KIF5C (OMIM 604593). Their individual contribution to the phenotype of the patient is discussed.

2 | CLINICAL PRESENTATION

This male infant is the second child born to a healthy nonconsanguineous 29-year-old mother and a 31-year-old father. The proband has a 9-year-old healthy sister. Family history is unremarkable. Pregnancy care showed no history of exposure to teratogenic or infective agents. At end of the 35th week of gestation, the mother presented with premature rupture of membranes. An antenatal ultrasound scan detected multiple anomalies with normal 46, XY chromosomes on cordocentesis at low chromosomal banding resolution of 400. The preterm infant was born by spontaneous vaginal delivery at 36 weeks of gestation with a birth weight of 3.3 kg (50th centile), a length of 54 cm (>95th centile) and head circumference of 33 cm (5-10th centile). At birth examination, he had dysmorphic features that included hypertelorism, prominent nasal bridge, exophthalmos, low-set ears with posterior rotation, micrognathia, short neck with redundant nuchal skin, clenched hands, hypospadias and cryptorchidism, sacral dimple, and rocker-bottom feet (Table S1).

 Shortly after birth the patient was transferred to the Neonatal Intensive Care Unit (NICU). Respiratory distress, spiked fever, and a cardiac murmur were detected. Echocardiogram (ECG) showed complex heart malformations consisting of double outlet right ventricle (DORV), ventricular septal defect (VSD), hypoplastic left ventricle and mitral valve, and Patent ductus arteriosus (PDA). Brain magnetic resonance imaging suggested total agenesis of the corpus callosum (Table S1).

 His abdominal ultrasound showed abnormal configurations of the gallbladder with multiple septations and multiple intraluminal echogenic foci, and bilateral hydronephrosis (grade III on the right and grade II on the left). On the 2nd day of life the patient developed seizures, with episodes of status epilepticus, that responded to anticonvulsant medication. He developed thrombosis of the right internal jugular vein and common iliac vein that required heparin administration. The patient also developed thrombocytopenia that required platelet transfusion. Complex congenital heart problems led to lung congestion that required prolonged high ventilation settings with inhaled nitric oxide therapy and full inotropic support. The patient died of hypoxic respiratory failure in the fourth week of life (Table S1).

3 | METHODS

Detailed demographic and clinical data (symptoms, time of onset of symptoms, physical and radiological examination) and sample collections were obtained from the patient during his admission to NICU for medical evaluation and according to King Abdulaziz Medical City (KAMC) protocol following the Saudi Ministry of Health (MOH) guidelines. Samples for aCGH were obtained from the patient and his parents.

Both chromosomal studies and aCGH were performed at the division of Molecular Pathology and Genetics, Department of Pathology and Laboratory Medicine, KAMC, Riyadh.

High-resolution chromosome (prometaphase) analysis on peripheral blood cultures was performed according to standard cytogenetic protocols following the International System for Human Cytogenetic Nomenclature (ISCN, 2016).

For array CGH analysis high-quality genomic DNA was extracted from the collected peripheral blood using QIASymphony kit (Qiagen) following standard manufacturer’s instructions. DNA quality was evaluated by Nanodrop ND-1000 (Thermo Wilmington), then fragmented, amplified, and hybridized using the CytoScan HD array platform (Affymetrix) and scanned with GeneChip scanner. Affymetrix CEL files were generated by the AffymetrixGeneChip® Command Console software (Affymetrix) and analyzed using the AffymetrixChASv3.2 software program. The software compares patient DNA hybridization to oligonucleotide and SNP probes of normal samples and the CNVs were mapped to the genome build GRCh38/hg19 for analysis and interpretation. In genomic imbalance, size of CNV, gene content and location were assessed in the interpretation. DECIPHER (https://decipher.sanger.ac.uk) (Firth et al., 2009), DGV (http://dgv.tcg.ca) (MacDonald, Ziman, Yuen, Feuk, & Scherer, 2014), ENSEMBL (https://asia.ensembl.org), OMIM (https://www.omim.org), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed) were used to evaluate the significance of the detected CNVs.

4 | RESULTS

High-resolution routine chromosomal analysis revealed a karyotype of 46,XY,del(2)(q23.1q23.3) at banding resolution.
FIGURE 1  G-banded chromosomes and array CGH analysis. High-resolution chromosomal analysis revealed a male karyotype with 46,XY del(2)(q21.1q23.3) at banding resolution of 550. Chromosome 2 ideogram highlights the proposed microdeletion cytogenetic genomic segment. Array CGH illustrates the 18.5 Mbp CNV deletion that appears in red color. Haploinsufficiency genes that apparently contribute to the patient's phenotype

- Gimelli et al., 2014, reported patient with:
  - 2q21.1 deletion
  - Psychomotor delay, language difficulties, Behavior impairment, scaphocephaly, prominent ears, bilateral shortness of the first metacarpal bone of the hand with proximally set thumbs, increased length of the bone elements of the first left toes resulting in one onghalluces with varus deformity, and bilateral cryptorchidism.

- Mulatinho et al., 2012, reported patient with:
  - 2q22.1-q22.3 deletion
  - Global developmental delay, lack of speech, balanic hypospadias, an omphalocele, coarse face with deep-set eyes, thick eyebrows, protruding tongue, small teeth, pointed chin, bulbous nose, wide spaced and hypoplastic nipples, scoliosis, bilateral clinodactyly of the fifth finger and bilateral cryptorchidism.

- Van Bon et al., 2010 reported 11 patients with:
  - 2q23.1 deletion
  - Mentally retarded with pronounced speech delay and additional abnormalities including short stature, seizures, microcephaly and coarse facies (2q23.1 deletion Syndrome).

- Noh and Graham 2012 reported 2 patients with:
  - 2q23.1 microdeletion
  - Seizures, developmental delay and distinct dysmorphic features.

- Bravo-Oro et al., 2015, reported patient with:
  - 2q22.3-2q23.3 deletion
  - 2q23.1 deletion syndrome features including absence of halluces, pure red cell aplasia, and intestinal aganglionosis.

- Almuzzaini et al., 2019, (current case) patient with:
  - 2q21.1-2q23.3 deletion
  - Dysmorphic features that include hypertelorism, prominent nasal bridge, exophthalmos, low-set ears with posterior rotation, micrognathia, short neck and excessive skin in the occiput, clenched hands, hypospadias and cryptorchidism, sacral dimple and rocker-bottom feet, and agenesia of the corpus callosum, congenital cardiac defects, bilateral hydronephrosis, spontaneous intestinal perforation.

FIGURE 2  Summary of significant reported cytogenetic breakpoints associated with chromosome 2 band q21.1-23.3
of 550 (Figure 1a). A high-resolution array CGH revealed a heterozygous interstitial deletion of 18,483 kb on cytogenic band 2q21.1–23.3 (Figure 1b,c) at genomic position (chr2:131,839,167–150,327,391). The chromosomal constitution was reported as 46,XY.arr[GRCH38]2q21 .2q23.3(131,839,167_150,327,391)x1. This 18.5 Mb deletion encompasses 56 genes. Array CGH on the parents was normal.

5 | DISCUSSION

We believe that this novel interstitial deletion encompassing 2q21.1-q23.3 genomic chromosomal regions has contributed significantly to the patient’s phenotype. The cytogenetic breakpoints and phenotype of patients with reported deletions within region 2q21.1-q23.3 are summarized in Figure 2. In our patient, array CGH analysis showed a deletion of approximately 18.5Mb at 2q21.1-q23.3, a region that includes 56 genes with 38 protein-coding genes. Of those genes, ZEB2, MBD5, and KIF5C cause recognizable clinical syndromes when one allele is mutated or deleted (Table S2).

Haploinsufficiency of ZEB2 causes Mowat–Wilson syndrome [MWS, OMIM 235730], a syndrome characterized by intellectual disability, delayed motor development, epilepsy, microcephaly, characteristic facial features, heart defects, genitourinary malformations, and Hirschsprung disease (Kluk et al., 2011; Mowat et al., 1998; Mowat, Wilson, & Goossens, 2003). Various sizes of deletions have been reported describing a MWS cases with deletion distal or upstream to the ZEB2 gene, proposing a possible disturbance of regulatory elements (Ballarati et al., 2009; Bravo-Oro et al., 2015; Garavelli et al., 2009; Mowat et al., 2003; Saunders, Zhao & Ardinger, 2009).

MBD5 haploinsufficiency is associated with typical manifestations of 2q23.1 microdeletion syndrome [OMIM 611472] (Talkowski et al., 2011) which is characterized by variable clinical presentations including microcephaly, intellectual disability, seizures, mild dysmorphic features, behavioral issues, and autistic-like features.

KIF5C heterozygous missense mutations are associated with complex cortical dysplasia and other brain malformations [OMIM 615282](Poirier et al., 2013; Willemsen et al., 2014).

6 | CONCLUSION

We describe a de novo interstitial deletion of 2q21.2-2q23.3. This genomic segment contains 56 morbid genes, 38 of which have a reported phenotype in OMIM. Our patient has some clinical findings described in patients with deletion of ZEB2, MBD5, and KIF5C genes but he also has clinical findings not previously described in patients with deletions involving this region of 2q. This may be due to some, as yet, undiscovered genes in the region or may be caused by other factors such as epigenetic effects occurring as a result of this large deletion.

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CONFLICT OF INTEREST

None declared.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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