

CASE REPORT

A Case Study of Distinctive Phenotypes Arising From Emanuel Syndrome in Two Karyotypically Identical Patients

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ABSTRACT

Emanuel syndrome, also referred to as supernumerary der(22) or t(11;22) syndrome, is a rare genomic syndrome. Patients are normally presented with multiple congenital anomalies and severe developmental disabilities. Affected newborns usually carry a derivative chromosome 22 inherited from either parent, which stems from a balanced translocation between chromosomes 11 and 22. Unfortunately, identification of Emanuel syndrome carriers is difficult as balanced translocations do not typically present symptoms. We identified two patients diagnosed as Emanuel syndrome with identical chromosomal aberration: 47,XX,+der(22)t(11;22)(q24;q12.1)mat karyotype but presenting variable phenotypic features. Emanuel syndrome patients present variable phenotypes and karyotypes have also been inconsistent albeit the existence of a derivative chromosome 22. Our data suggests that there may exist accompanying genetic aberrations which influence the outcome of Emanuel syndrome phenotypes but it should be cautioned that more patient observations, diagnostic data and research is required before conclusions can be drawn on definitive karyotypic-phenotypic correlations.

Keywords: Emanuel syndrome, Karyotyping, Translocation, Karyotype phenotype correlation

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INTRODUCTION

The phenotypic presentations of Emanuel syndrome is believed to stem from the der(22) supernumerary marker chromosome (SMC) which is generated through 3:1 meiotic disjunction of a parental balanced translocation between chromosome 11 and 22 during gametogenesis. The syndrome is known by other names, including derivative 22 syndrome, supernumerary der(22)t(11;22) syndrome and partial trisomy (11;22), which indicates the presence of 47, instead of the usual 46 chromosomes in the cells of the body. This genomic syndrome was discovered in 2004 by the cytogeneticist Dr Beverly Emanuel in Philadelphia, USA.

Emanuel syndrome is usually discovered in infants and manifests in many ways, which often includes

profound intellectual disabilities, microcephaly, failure to thrive, hypotonia (weak muscle tone), preauricular or sinus tags, ear anomalies, cleft or high-arched palate, micrognathia, renal anomalies, congenital cardiac defects, down-slanting palpebral fissures and abnormal auricles. In males, genital abnormalities are also known to develop. There have only been approximately 100 reported cases of Emanuel syndrome in scientific literature and only one case reported in Malaysia (1).

The management of patients with Emanuel syndrome is difficult due to the considerable multiple and varied physical and mental disabilities. Karyotypic and phenotypic correlations have been inconsistent and difficult with no known comparable cases with identical karyotypes within a defined population published thus far. Here we report two cases of karyotypically identical Emanuel syndrome patients presenting with vastly different phenotypic outcomes in the Malaysian population.

CASE REPORT

Patient 1:

We received the blood sample taken from a newborn baby at day 1 after birth referred for karyotyping at the

Advanced Diagnostics Laboratory (ADL). The patient was found to have congenital deformities including low-set ears with skin tags, undersized jaws (micrognathia) and calcaneovalgus feet. Her blood sample was sent for cytogenetic analyses and it was revealed that she has an abnormal karyotype of 47,XX,+der(22)t(11;22)(q24;q12.1)mat (Figure 2(a)). Fluorescent in situ hybridization (FISH) analysis of the patient’s sample using whole-chromosome paint probes on chromosome 11 and the q terminal of chromosome 22 was performed for further confirmation (Figure 2(b)). The infant is the second child of her parents; neither her mother nor her grandmother were affected by Emanuel syndrome (Figure 1(a)). The origin and traits of the extra SMC [der(22)t(11;22)(q24;q12.1)] was confirmed by chromosomal analysis of the girl’s parents, and the mother, who was found to be a balanced translocation carrier had a karyotype of 46,XX,t(11;22)(q24;q12.1). Further, the aunts of the patient were also advised to undergo karyotyping tests. Two of her aunts were determined to be positive balanced translocation carriers. The balanced translocation was found to be inherited from the patient’s immediate family.

Patient 2:

We received the blood sample taken from a newborn baby at day 1 after birth, which exhibited similar phenotypical manifestations as Patient 1, including micrognathia and low-set ears. In addition, a flat nasal bridge, webbed neck, bilateral dislocatable radius and ulna, wide spread nipples, limited hip adduction, high-arched palate, prominent occiput, microcephaly and bilateral preauricular pits were also observed in the patient. Cytogenetic analysis confirmed the chromosomal abnormality with 47,XX,+der(22)t(11;22)(q24;q12.1)mat, indicating that the baby girl had Emanuel syndrome. The infant’s family background did

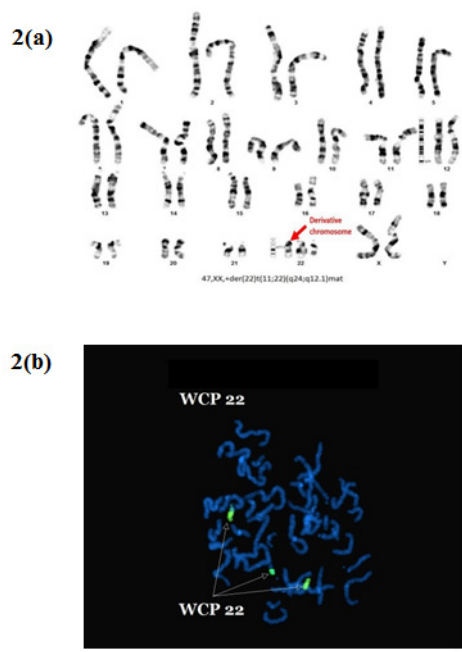


Figure 2: (a) Karyotyping results of Patient 1 revealed the existence of an extra supernumerary chromosome. (b) Fluorescent in situ hybridisation results indicating probing of chromosome 11 and the q terminal of chromosome 22 (green)

not reveal a history of Emanuel syndrome (Fig. 1(b)). Karyotyping with G-banding analysis at 400 band levels identified that the patient had an SMC der(22) derived from a translocated chromosome 22. To confirm the findings, karyotyping was performed on the patients’ parents. As the mother was found to be a balanced translocation carrier with 46,XX,t(11;22)(q24;q12), the SMC in the newborn case was confirmed to originate from her mother.

DISCUSSION

About 9% of all SMCs are derived from chromosome 22. This chromosome can undergo numerous rearrangements, resulting in a host of genetic disorders and developmental anomalies. While they are usually asymptomatic, balanced carriers may also report problems such as recurrent pregnancy loss, male infertility and the birth of offspring with imbalanced chromosomes. Babies born from carrier mothers may develop Emanuel syndrome or supernumerary der(22)t(11;22) syndrome resulting from 3:1 meiotic malsegregation of der(22). Malsegregation during meiosis occurs when the sister chromatids fail to migrate in equal numbers to the centrosomes at opposite poles of the dividing cell, resulting in the unbalanced segregation of chromosomes in the daughter cells. The clinical symptoms of Emanuel syndrome are attributed to the duplication of 22q10-22q11 and 11q23-11qter on the supernumerary derivative chromosome 22. Furthermore, over 99% of all reported cases of Emanuel syndrome indicate that one of the parents is a balanced carrier of t(11;22) and is physically normal. The overall prevalence of Emanuel syndrome worldwide has been

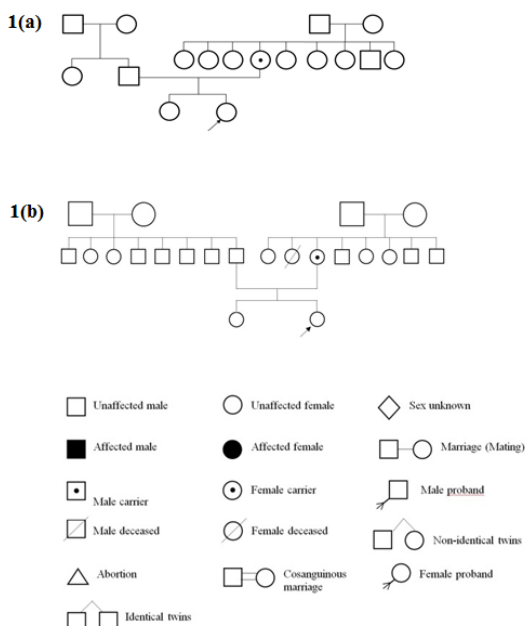


Figure 1: The family pedigree of (a) patient 1 (b) patient 2

estimated to be 1 in 110,000 (2).

The two cases of Emanuel syndrome identified by our diagnostic center share an identical karyotype while displaying vastly differing phenotypes. As evident in Table 1, the phenotypic presentation of Patient 1 is significantly milder compared to Patient 2. The first patient identified in 2012 was reported to have low-set ears with skin tags, undersized jaws (micrognathia) and calcaneovalgus feet. The second patient, diagnosed two years later, presented similar symptoms to patient 1 aside from the calcaneovalgus feet. In addition, a flat nasal bridge, webbed neck, bilateral dislocatable radius and ulna, wide spread nipples, limited hip adduction, high-arched palate, prominent occiput, microcephaly and bilateral preauricular pits were also observed in the patient. It is also noteworthy that the disorder was passed down through asymptomatic maternal carriers with identical t(11;22) translocations. Previous literature has disclosed that Emanuel syndrome patients display variable physical and mental phenotypes and karyotypes have also been inconsistent aside from the presence of a derivative chromosome 22. In fact, the first patient in Malaysia to be reported with Emanuel syndrome also presented differing phenotypes from our two cases which included malformed ears, micrognathia, high-arched palate, preauricular pits and supra-auricular skin tags (1).

The vast diversity of manifestations amongst patients has been previously reported. Moreover, the additional disclosure of novel presentations widens the phenotypic spectrum of Emanuel syndrome indications (3). A new method of clinical diagnosis using next-generation phenotyping has opened a novel avenue in identification of Emanuel syndrome patients. This technique utilizes facial dysmorphology novel analysis (FDNA) technology to automatically identify possible Emanuel syndrome patients from 2D facial photos (4). It is also disclosed that this recognition technique is able to distinguish between closely related disorders resulting from SMCs. Further, a case report by Luo et al (5) described that the additional use of SNP-array analysis identified two pathogenic duplications, which involved 22q11.1-q11.21 (3.1Mb) and 11q23.3-q25 (18.2Mb),

Table 1: Comparison of phenotypic abnormalities between an earlier reported case in Malaysia and the current study

Clinical features	Afroze et al 2008 (5)	Patient 1	Patient 2
Ears low/malformed	+	+	+
Micrognathia	+	+	+
Microcephaly	-	-	+
Palate high-arched	+	-	+
Preauricular pits	+	-	+
Neck short/webbed	-	-	+
Wide spread nipple	-	-	+
Flat/broad nasal bridge	-	-	+
Calcaneovalgus feet	-	+	-
Supra-auricular skin tags	+	-	-

respectively. These aberrations have been linked to the presentation of various phenotypes including mental disabilities and other congenital abnormalities. These findings highlight that high-resolution molecular techniques, including array comparative genomic hybridization (aCGH) and next-generation sequencing (NGS), may be able to provide additional information on genetic anomalies such as mutations, micro-deletions, SNPs and copy number variants which may contribute to better genotypic-phenotypic correlations in Emanuel syndrome patients. Taken together, these data suggests the need for further clinical evaluations following initial diagnosis to improve overall management of patients with the eventual aim of improving their quality of life.

CONCLUSION

To our knowledge, this is the first comparative case study in Malaysia involving two patients with identical Emanuel syndrome karyotypes having vastly differing phenotypic presentations. The basis of this disorder stems from the der(22) SMC but phenotypic presentations could be influenced by additional genetic aberrations. It is hoped that the disclosure of this case study would increase the awareness of clinicians on the need to refer dysmorphic cases for cytogenetic analyses. In addition, it is expected that reports such as this are able to contribute to further research aimed at better understanding Emanuel syndrome karyotype-phenotype correlations which has thus far been difficult to establish.

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