Exome sequence identifies a cryptic chromosome translocation in a family decades after clinical diagnosis of Cornelia de Lange: case report

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Abstract

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Written informed consent was obtained from the patient to publish this case report, in accordance with the Journal's patient consent policy.

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Abstract

Clinical genetic evaluations are defined by the knowledge and technology available at the time they occur. In the modern era, microarray and exome sequence are first line tests for clinical geneticists; however, beginning in the late 1970s and continuing until the turn of the past century, a standard genetic evaluation consisted, in many cases, of an examination by a dysmorphologist as well as a conventional karyotype. In general, once a genetic diagnosis is established, it does not get revisited as more advanced methods become available. Clearly, there will be instances in which new technology can modify or change a prior diagnosis. We present a family in which the recent birth of a baby resulted in the establishment of a cytogenetic diagnosis of a different family member whose initial evaluation and clinical diagnosis had occurred three decades earlier. The new genomic findings have profound implications for other family members, and in addition provided the family with a sense of closure.

Case Report

The proband is a healthy 35-year-old currently G9P4054 who presented after the demise of her second baby to discuss reproductive options. Prior to her first pregnancy, she had sought genetic counseling because of her striking family history. Her older sister (Figure 1B and II 6 in Figure 3), who was profoundly impaired, carried the diagnosis of Cornelia de Lange syndrome, and because Cornelia de Lange syndrome is most often due to de-novo dominantly acting mutations, she was reassured that recurrence was unlikely. She also reported that she had had identical twin brothers, born at 28 weeks gestation (Figure 2, I 1 and 2). One twin died in infancy, while the other survived until age 20 with severe cognitive impairment (Figure 1C). Because her brother's impairment had been ascribed to complications of severe prematurity, she was reassured that this too was unlikely to recur. Her first pregnancy was uneventful and ended in the full-term delivery of a healthy female infant. During her second pregnancy, ultrasound showed normal fetal anatomy in the second trimester and fetal growth restriction in the third trimester. After an uncomplicated vaginal delivery, the female infant was noted to be small for gestational age (SGA) at 2,005 grams, and was noted to have microcephaly, a high arched palate, widely spaced eyes, a low set right ear and a wide sacral dimple (Figure 1A). Multiple rib and vertebral anomalies were seen on X-ray, and bilateral ankle eversions were noted. Echocardiogram revealed an atrial septal defect, patent ductus arteriosus, tricuspid regurgitation, and poly-valvular thickening. The infant was admitted to the neonatal intensive care unit at 18 hours of life with concern for seizures. Electroencephalography (EEG) was not consistent with seizures, but capillary blood gas revealed severe metabolic acidosis with a pH of 6.76. Despite appropriate therapy, the acidosis was unremitting. Lactic acid was $>$ 24 mmol/L and ammonia was mildly elevated at 218 micromole/L. Evaluation for possible inherited causes of metabolic acidosis was undertaken, however, no cause was identified. The infant died at 51 hours of life. The presumed cause was an inborn error of metabolism, with the differential including pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency or holocarboxylase deficiency. An autopsy was performed, and notable findings included diffuse lipid vacuolization in hepatocytes, small kidneys, an atrial septal defect, and hypoplasia of the corpus callosum. Enzyme studies performed on fibroblast cultures from skin showed normal enzyme activity for pyruvate dehydrogenase and pyruvate carboxylase.

Because a recessively inherited cause for metabolic acidosis was suspected, whole exome sequencing of the mother, father and baby was undertaken. Potentially causative sequence variants were not identified, but a sub-telomeric duplication of 12 Mb of chromosome 6q26q27 (chr6:161696380-170911240), in conjunction with a deletion of 11.7 Mb of distal chromosome 1q43q44 (chr1:237461414-249168732) was reported. This finding led to the cytogenetic investigation of both parents using sub-telomeric FISH probes for chromosomes 6q and 1q. The mother was identified as a carrier of an apparently balanced translocation between distal chromosome 6q and distal chromosome 1q, consistent with the deletion/duplication present in her child (Figure 2). Both the deletion and the duplication contained multiple genes and provided a sufficient explanation for the growth restriction, malformations, and dysmorphic features. However, a definitive explanation for the fatal metabolic acidosis was not identified.

The patient was informed of the substantial risk of chromosome imbalance in future pregnancies, and conventional prenatal diagnosis with CVS and microarray as well as IVF with preimplantation aneuploidy testing were offered. During this discussion, it was noted that chromosome imbalance due to a parental translocation might be the explanation of both of her siblings' severe cognitive impairment. Her sister's evaluation that resulted in the diagnosis of Cornelia de Lange syndrome had occurred many years earlier, long before the availability of microarray, and her brother had never received a genetic evaluation.

With this possibility in mind, the patient's parents were cytogenetically evaluated using sub-telomeric FISH probes, and her mother (I 1 in Figure 3) was found to carry the translocation. This knowledge prompted the testing of the sister with de Lange Syndrome, who was shown to have the same chromosome 1q deletion/6q duplication that was identified in the proband's deceased daughter. Neither of the proband's unaffected siblings carried the translocation. She conceived a 3rd pregnancy that was evaluated by CVS/microarray at 11 weeks gestation and was found to have partial 1q deletion and 6q duplication, consistent with the translocation. She elected to terminate the pregnancy. Unfortunately, her 4th pregnancy was similarly affected, and again, she elected termination. She had an unaffected 5th pregnancy with a term spontaneous vaginal delivery. Her 6th pregnancy resulted in a spontaneous abortion that occurred prior to genetic evaluation, and

her 7th and 8th pregnancies were shown by CVS/microarray to be affected by the 1q deletion/6q duplication, resulting in elective termination. Most recently, her 9th pregnancy resulted in an uncomplicated cesarean delivery of dichorionic diamniotic twins following 1sttrimester CVS that confirmed normal microarray results for both twins.

Discussion:

The discovery of the chromosome translocation was an important event for this family, given the role this new diagnosis had in their lives. The proband's mother stated that she immediately recognized the similarities between her daughter with Cornelia de Lange syndrome and her now deceased granddaughter. She describes having a strong suspicion that her daughter and granddaughter were affected by the same condition, and she felt a profound sense of closure after learning of the chromosome abnormality and its role in both her daughter and deceased granddaughter. She suspected that her deceased twin sons were affected with the chromosome abnormality as well.

Chromosome aberrations that result from abnormal segregation of parental balanced chromosome rearrangements are a well-known cause of abnormal development. However, a standard karyotype performed on the proband's sister in the late 1980's failed to detect the chromosome imbalance because of the "cryptic" subtelomeric location of the breakpoints. Literature search did not identify other cases with a similar balanced translocation or a similar combination of distal 1q deletion/6q duplication, and thus, there is no clear basis for prediction of likely phenotypic features. However, the phenotypic spectrum associated with distal deletion of chromosome 1q is known to include cognitive impairment, growth retardation, microcephaly, agenesis of the corpus callosum and distinctive facial features (van Bon, Koolen et al. 2008). Thus, the features present in II.1 (the proband's sister) are consistent with 1q deletion. In addition, some of the features of III.1, such as hypoplastic corpus callosum are consistent with 1q deletion. The phenotypic effect of the distal 6q duplication is difficult to evaluate, since we were not able to identify any reports with a similar duplication. It seems likely that a duplication of this size, containing 39 genes, contributed to the clinical picture.

The proband's sister received the diagnosis of Cornelia de Lange syndrome prior to any knowledge of the molecular genetic basis for this condition. Now we know that most cases of de Lange syndrome are due to point mutations in NIPBL (Musio et al., 2006); however, there are several reports describing de Lange syndrome in children with various segmental aneuploidies (DeScipio, Kaur et al. 2005). We note one such case which had a distal 1q deletion that is similar to the one we report (Borck, Redon et al. 2004). Thus, the diagnosis of de Lange syndrome in the proband's sister was not necessarily incorrect. However, the reassurance given to the family that the condition was unlikely to recur turns out to have been incorrect. As the proband's children reach reproductive age, they will be duly informed about the possibility of being carriers of a chromosome translocation.

Interestingly, the outcomes of the two individuals with 1q deletion/6q duplication were quite different, with one living into adulthood and the other dying in the neonatal period. This observation raised the concern that the proband's daughter may have had a second diagnosis, explaining the lethal metabolic acidosis. To address this possibility, we questioned whether any genes in the 1q deletion region or the 6q duplication region might plausibly have contributed to the acidosis. Specifically, we re-reviewed the exome data to identify whether the proband's father harbored any deleterious variants in any of the genes in the 1q deletion region; however, none were identified. The chromosome 6q duplication region was noted to contain the gene BRP44L, in which homozygous loss of function results in pyruvate carrier deficiency (OMIM 614741), a known cause of metabolic acidosis. However, it is difficult to understand how the presence of three copies of this locus might lead to complete loss of function. Also, as noted above, biochemical studies on cultured fibroblasts did not identify any evidence of abnormal pyruvate metabolism. At this point, we do not have an adequate explanation for the profound metabolic acidosis.

It is tempting to speculate that the twin children (II 1 and II 2 in Figure 3) may also have been affected by a chromosome imbalance due to the parental translocation. However, given their severe prematurity, non-specific phenotypic features and demise many years ago, the answer to this question is likely to remain

a mystery.

This case illustrates the value of revisiting old diagnoses using new technology, especially when recurrence is a possibility.

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Figure Legends

Figure 1:

1. The proband's second daughter, born with multiple malformations.
2. The proband's sister with Cornelia de Lange syndrome.
3. The proband's brother, with severe developmental delay but no specific diagnosis.

Figure 2:

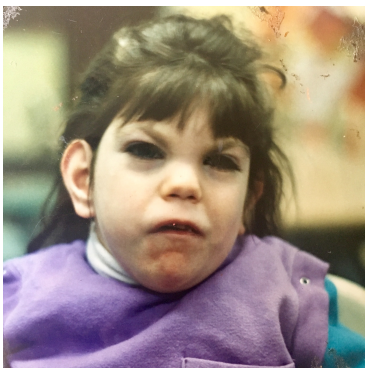
Ideogram of chromosomes 1 and 6, with arrows indicating the position of breakpoints in the subtelomeric region of both chromosomes. Partial karyotype of proband with arrows indicating the position of breakpoints.

Metaphase FISH studies of the proband, showing that the 1q subtelomeric probe identifies the 6q telomeric region and the 6q subtelomeric probe identifies the 1q subtelomeric region, indicating a translocation between 1q and 6q.

Figure 3:

Pedigree of the family showing the proband (II 5), her mother (I 1), her affected sister (II 6) and her deceased daughter (III 2)

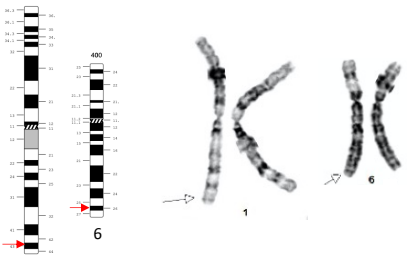
A. 



B.

C. 

A.



B.