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De novo duplication 4(q21-q28) in sibs, as a possible ovarian germinal mosaicism, more clinical analysis delineation

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Table 1 to 3 are available in the Supplementary Files section.

De novo duplication 4(q21-q28) in sibs, as a possible ovarian germinal mosaicism, more clinical analysis delineation

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Short title: De novo duplication 4(q21-q28) in sibs due to ovarian germline mosaicism.

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ABSTRACT

Two additional cases are described with partial trisomy 4q, resulting from a de novo duplication of chromosome 4, involving segments q21-q28. This time a sibling is affected. The clinical manifestations are similar to other cases with de novo 4q duplication involving the same segments. Although a single distinctive phenotype has not been established, most reported cases of de novo duplication share a similar clinical spectrum depending on the specific duplicated segment of chromosome 4q.

The major clinical manifestations are growth and psychomotor retardation, microcephaly, epicantic fold, antimongoloid slant of palpebral fissures, low-set and malformed auricles, high nasal bridge, long philtrum small mouth, micrognathia, short neck, additionally, one patient presented congenital heart disease, and both presented congenital pyloric hypertrophy stenosis, dorsal edema of the hands and feet, the hypertrichosis as the most important clinical manifestations. Diverse genes involved in neural, cardiovascular, acrorenal, and skeletal development—identified in molecular studies of the duplication—are reviewed; these genes are potentially responsible for the phenotypic anomalies reported in each chromosomal region. We reported the another family directly affected with the same de novo direct duplication in the literature of a rare chromosomal trisomy, as the second ovarian germline mosaicism case which was demonstrated through cytogenetic and molecular analysis, confirmed by fluorescent in situ hybridization (FISH) with a painting probe and microsatellites studies. Besides, deep in a clinical analysis of karyotype-phenotype correlation in each duplicated segment.

Key words: Dir Dup 4q, Interstitial duplication 4q, de novo duplication 4q in sibling, Clinical phenotype in trisomy 4q, Trisomy 4q, Trisomy 4q syndrome, Germinal mosaicism.

INTRODUCTION

Chromosomal germinal mosaicism is rare and occurs in early germ cells before the onset of meiosis. These mitotic errors can be nondisjunctions or the production of structural rearrangements (deletion, duplication, inversion, insertion or translocation). Germinal mosaicism becomes evident when two siblings are born with the same de novo chromosomal abnormality. Trisomy 4q is a rare chromosomal rearrangement resulting predominantly from translocations and almost always accompanied by another rearrangement that does not define a specific clinical syndrome. Pure trisomies are even rarer—with just over 20 cases described—and a distinct clinical syndrome has not yet been defined; however, associations have been proposed based on the duplicated fragment, and molecular studies in these cases have helped identify the genes involved that contribute more specifically to the phenotype.[1-23]

The clinical manifestations are similar to other cases with de novo 4q duplication involving the same segments. Although a single distinctive phenotype has not been established, most reported cases of de novo duplication share a similar clinical spectrum depending on the specific duplicated segment of chromosome 4q. Recent molecular studies of cases involving duplication have identified genes implicated in development—primarily neuronal, but also vascular, renal, and musculoskeletal.[11,14,19,22]

There are several reported cases of partial trisomy 4q; it is an uncommon chromosome abnormality and most cases result from familial balanced translocations. The translocation shows events of partial deletion and/or duplication involving diverse chromosome fragments, which prevents a clear determination of the correlation between phenotype and karyotype. A thorough and detailed analysis of de novo or single duplication fragments, alongside their clinical features, could explain a possible delineated 4q trisomy syndrome. Scarce reports with a high variability of phenotypes and duplicated segments have hindered the analysis; early

cohorts were limited to twenty-three cases of 4q duplications,[1-22] and while early cohorts were limited, over 60 cases of partial trisomy 4q have now been documented in total.[23] Other cases present as a mosaic and offspring of a previous duplicated chromosomal abnormality.

There are many familial reports with 4q trisomy but only a few more than a 30 cases with a pure duplication, all of which resulted from different paternal rearrangements. A possible breakpoint and recombination site rendering the rearrangement recurrent has been suggested. A syndrome linked to potential developmental genes within the duplicated segment has been suggested. Recent molecular studies of cases involving duplication have identified genes implicated in development—primarily neuronal, but also vascular, renal, and musculoskeletal.[11,14,19,22]

This is the second report of de novo duplication in siblings suggestive of maternal germline mosaicism. We describe two sibling cases with the same clinical characteristics and de novo direct interstitial duplication of segment 4q21-q28, a rearrangement that has been reported once previously.[10] Added a review of the literature and explore the karyotype-phenotype correlation according to each segment involving in the pure duplications.

MATERIAL AND METHODS

CLINICAL REPORT

Patient 1

The first child was the proposita, a girl born after 38 weeks of gestation to a 16-year-old mother and a 35-year-old father, both apparently healthy and non-consanguineous. The pregnancy was uneventful with good prenatal control, delivered by cesarean section due to cephalopelvic disproportion. Her birth weight was 2850 g (10th centile), length was 49 cm (50th centile), and OFC was 30 cm (<3rd centile). Apgar scores were 4 and 6 at one and five minutes, respectively. She was hospitalized for asphyxia for one week, underwent emergency surgery performed at birth for congenital hypertrophic pyloric stenosis, and was diagnosed with congenital heart disease (patent ductus arteriosus). The patient required five hospitalizations up to 42 months of age, including two admissions for pneumonia, one for seizures, and recurrent urinary tract infections. Psychomotor and cognitive development was severely delayed. She had muscular hypotonia and generalized tonic-clonic seizures. Clinical examination at age 3 years and 6 months revealed: weight 11.65 kg (<3rd centile), length 92 cm (3rd centile), and OFC 42 cm (<3rd centile).

She presented with microcephaly, brachycephaly, a prominent metopic ridge, a hirsute forehead, thick eyebrows, synophrys, and a high nasal bridge. Her eyes showed bilateral palpebral ptosis, hypotelorism with convergent strabismus, bilateral epicanthic folds, and upslanting palpebral fissures (similar to the mother); a long philtrum; and small, downturned angles of the mouth.

Dental malocclusion and micrognathia were noted, along with a high-arched palate. The ears were large, low-set, and posteriorly rotated with a prominent helix and antihelix; the left ear

showed a wide concha. Short neck and a low hairline were present. The thorax was broad with widely spaced nipples (Figure 1a).

She presented with edema on the dorsum of the hands and feet, brachydactyly, hypoplastic nails, and bilateral single transverse palmar creases. Further anomalies included an inguinal hernia and dysphagia without esophageal abnormalities. The girl died one month later from pneumonia.

Patient 2

The second patient was the 2-year-old younger brother of the proband. He was described by his mother as having the same clinical features as his sister. The pregnancy was uneventful; delivery was by cesarean section at 39 weeks of gestation. The boy was hospitalized at birth and required emergency surgery due to congenital hypertrophic pyloric stenosis. Cardiology examination was normal. Psychomotor and cognitive development was moderately delayed, and neonatal hypotonia was noted.

Clinical examination at 2 years and 2 months of age showed: weight 10.89 kg (<3rd centile), length 85.7 cm (25th centile), and OFC 45 cm (<3rd centile).

The head was microcephalic and brachycephalic; the forehead was prominent with hirsutism and thick eyebrows. The eyes showed an antimongoloid slant with short palpebral fissures, palpebral ptosis, slight convergent strabismus, and bilateral epicanthic folds. He presented an upturned nose, a high and broad nasal bridge, long philtrum, small mouth with downturned angles, prominent upper lip, high narrow palate, macroglossia, and dental malalignment. The ears were large, low-set, posteriorly rotated, malformed with wide conchae and prominent helix and antihelix. He also presented micrognathia. The neck was short, with a low posterior hairline and mild generalized hirsutism (Figure 1b-d).

The dorsum of the hands and feet were edematous with brachydactyly, hypoplastic distal phalanges, nail hypoplasia, clinodactyly of the fifth fingers, and bilateral Sydney creases (Figure 1d).

Other anomalies included an umbilical hernia; cardiology examination revealed no congenital defects.

Psychomotor development showed mild delay, and his language skills at 25 months were severely delayed. He experienced seizures during his first six months of life, but remained seizure-free thereafter. He was able to stand but could not walk.

The children were offspring of a 20-year-old healthy mother, whose only findings were borderline short stature and mild psychomotor delay. The pedigree showed the children were from two different, unrelated fathers; all other children from their respective alternative partners were clinically normal.

CYTOGENETICS STUDIES

Chromosome studies from cultured blood lymphocytes using GTG banding revealed a direct duplication of 4q21-4q28 in both siblings (n=50 cells per patient) as the sole abnormality; the karyotype was 46, XX/XY, dir dup(4) (q21q28) (Figure 2a, b). The mother's chromosomes were normal in both lymphocyte (n=200 cells) and fibroblast (n=50 cells) cultures. The biological fathers were unavailable for testing.

FISH studies with a whole chromosome 4 painting probe (Oncor Inc. Gaithersburg, Maryland. USA), performed according to the manufacturer's manual confirmed that the extra material originated from chromosome 4 (Figure 2b). Fluorescent hybridization was performed on interphase cells (n=200) from maternal slides to evaluate for low-level mosaicism, but all were normal. Although this confirms a normal maternal karyotype in two distinct cell lines, it does

not exclude the possibility of germline mosaicism, as the mother may carry an unbalanced chromosome in her gametes.

Molecular studies

To determine the parental origin of the duplicated chromosome (given that both affected children had different fathers, suggesting the mother as the obligate carrier), we performed microsatellite analysis using multiplex PCR to the mother and the male infant, using a blood sample preserved on filter paper. The markers D4S394, D4S405, D4S414, D4S402, D4S424, D4S413, D4S415, D4S426, and FGA from CODIS (located at 4q28) were amplified and analyzed using an AmpFlSTR® Identifiler kit (Applied Biosystems, Foster City, California, USA).[16,24] Results were evaluated via capillary electrophoresis on an ABI PRISM 3130 genetic analyzer (Applied Biosystems), confirming the maternal origin of the abnormal duplicated chromosome (Figure in Annex).

DISCUSSION

Most cases of partial 4q trisomy result from an unbalanced segregation of a translocation, often inherited from the mother and occasionally from the father, an origin consistent with the greater resilience of oogenesis to structural rearrangements.[25,26] In our cases, the presence of an identical pure 4q21-q28 duplication in two siblings with different fathers, normal maternal somatic karyotype, and molecular microsatellite evidence confirms a maternal germline origin. Recurrent pure 4q duplications in siblings with normal parental somatic tissues have also been reported by Goodman et al.,[11] Otsuka et al.,[19] and Tosca et al.,[22] highlighting ovarian mosaicism as a key mechanism for familial recurrence, even when other chromosomes are involved in

translocations.[27] De novo pure 4q duplication has been documented in slightly over twenty cases (Tables 1-3).[1-4,6-8,10,11,14,16,19,22,28]

The delineation of specific clinical phenotypes in partial 4q trisomy remains controversial due to significant clinical and cytogenetic heterogeneity. Nevertheless, many clinical features are common to patients with partial trisomy 4q: developmental and growth delay, microcephaly, large, low-set, malformed ears, a wide and high nasal bridge, epicanthic folds, downward and narrow slanting palpebral fissures with ptosis, hirsute eyebrows, strabismus, downturned mouth corners, micrognathia, short neck, renal anomalies, and epilepsy. Less common features include thumb anomalies, congenital heart disease, hirsutism, low-set hairline, and synophrys. Many of these features were observed in our patients and have been reported in other de novo duplication cases.[6-8,10] Furthermore, some patients with "impure" 4q trisomy present with similar clinical features.[5,25,29-34,40]

According to the literature review, psychomotor delay and certain craniofacial and skeletal anomalies (particularly affecting the hands and fingers) are the most frequent findings associated with the most proximal segment, 4q1 (Table 1). Cases presenting with craniofacial anomalies alongside neurological and cardiovascular developmental defects more frequently involve segment 4q2 (Table 2), whereas urogenital and renal anomalies, as well as craniofacial and neurodevelopmental defects, are mostly related to 4q3 duplications (Table 3).[8,31]

Therefore, genes involved in acrorenal development appear to map distal to 4q31 rather than within 4q21-q22 as proposed by Hegmann et al.[34] This conclusion is supported by the lack of renal and thumb anomalies in our patients and in two additional reported cases whose duplications involved 4q2 rather than 4q3.[8,10] While Otsuka et al.[19] argued that renal hypoplasia is female-prone and maps to the distal 4q33-q34 region, recent studies by Zhuang et al.[23] reinforce that acrorenal anomalies correlate strictly with distal duplications that do not overlap

with our patients' 4q21-q28 segment. Three reported de novo cases involved segments of 4q2 and 4q3 (excluding q21q22 in one case),[1] all of which exhibited renal involvement.[1,2,7]

The recurrent urinary tract infections observed in Patient 1 may suggest subtle urinary tract involvement, as the duplicated 4q21-q28 interval contains genes implicated in renal development and function, including *PKD2, FRAS1, SHROOM3, FAT4*, and *BBS7*.[41-45] In a microsatellite analysis study, Binczak-Kuleta et al.[35] identified the *PKD1* gene at 4q21-23 in Polish families with autosomal dominant polycystic kidney disease. However, high-resolution array-CGH and SNP array studies demonstrate that structural acrorenal anomalies (such as renal hypoplasia and urogenital defects) require duplication of the distal 4q32–q35 region.[19,23,36,37]

The most recently reported case involved a premature infant with microcephaly, growth and developmental abnormalities, and urogenital anomalies—such as hypospadias, horseshoe kidneys, and abnormal kidney growth. A genetic study revealed a *de novo* 38 Mb duplication at 4q28.1-q32.3 (Table 2). 177 genes identified within the duplicated region, 26 were associated with phenotypic disorders, including those related to growth, development, and renal health; however, none were directly related to renal development, despite the q32 segment being involved. Thus, renal anomalies could arise from an influence or a secondary or indirect mechanism, such as a regulatory factor. The gene *NAA15* (N-alpha-acetyltransferase 15) was correlated with short stature, while *GRIA2* (Glutamate Ionotropic Receptor AMPA Type Subunit 2) and *INTU* (Inturned Planar Cell Polarity Protein) were associated with speech delay. Microcephaly was linked to *PLK4* (Polo-Like Kinase 4), a gene involved in cell cycle control and brain development.[46]

Zhuang et al. analyzed cases resulting from translocations involving gains of the long arm of chromosome 4, demonstrating the involvement of genes such as *TLL1* and *VEGFC* (responsible

for cardiovascular development) in anomalies associated with trisomy 4q syndrome.[23] The absence of structural renal malformations in our patients clinically confirms that nephrogenic development genes do not reside within 4q21–q28, establishing a clear boundary between proximal neurovascular manifestations and distal renal pathology.

Duplications involving the 4q21–q28 interval include dosage-sensitive genes involved in neurodevelopment, craniofacial morphogenesis, and cardiogenesis. Within 4q21.2–q21.3, functional and genetic evidence supports *AFF1* (AF4/FMR2 family member 1, formerly known as the AF4 gene for Central Nervous System development) and *SPARCL1* (synaptogenesis and prefrontal cortex function) as candidate contributors to intellectual disability, developmental delay, and craniofacial dysmorphism, while *DSPP* (dentin sialophosphoprotein*)* and *SPP1* (secreted phosphoprotein 1, also classically known as osteopontin) may contribute to connective tissue and extracellular matrix manifestations. More distal genes expressed during neurogenesis at 4q25, such as neurogenin 2 (*NEUROG2*, involved in neuronal differentiation) and 4q28.3 protocadherin-mediated cell adhesion (*PCDH10*), contribute to neurodevelopmental impairment, hypotonia, and congenital cardiovascular anomalies.[22,38]

Consistent with these observations, the duplicated interval in our patients includes several genes with established roles in neuronal development and synaptic function (*WDFY3*, *PPP3CA*, *GRID2*, and *MAPK10*) which may further contribute to the neurological phenotype. Additionally, *MAB21L2* (4q31), *PCDH18* (4q31), and *GRIA2* (4q32-q33) contribute to neurodevelopment in the 4q3 segment.[22]

The recurrence of identical breakpoints in siblings suggests a mechanism of recurrent genomic instability involving the 4q26–q28 region, potentially mediated by non-allelic homologous recombination. According to microsatellite analysis, an allelic crossover (4q26-q28) occurred during maternal gametogenesis, likely caused by intra- and interchromosomal recombination

during meiotic division.[22] Similar mechanisms have been observed in various chromosomal rearrangements involving other chromosomes, highlighting critical sites for structural rearrangements.[37,39]

This study of related cases is limited by the lack of detailed, high-resolution molecular mapping that would allow for a more in-depth analysis of the chromosomal rearrangement's behavior. Unfortunately, we do not have the specific study data available to conduct further analysis, as the material was a donation; regrettably, the patient passed away during the course of the study, leaving us without further samples to complete the analysis.

Nevertheless, the findings support this hypothesis based on the clinical-cytogenetic presentation. This represents the second confirmed case of ovarian germline mosaicism leading to duplication of the long arm of chromosome 4, underscoring a recurrent breakpoint associated with familial cases.

Our findings confirm that pure interstitial 4q21-q28 duplications delineate a distinct clinical phenotype, with recurrent familial cases pointing to cryptic maternal gonadal mosaicism. Future research should leverage high-resolution genomic profiling and transcriptomic analysis in larger cohorts to refine candidate gene networks within the 4q2 segment and elucidate the precise mechanisms driving gonadal non-allelic homologous recombination.

Undoubtedly, this familial case represents an extremely interesting example of a rare, not yet fully characterized chromosomal condition; it opens up debate and analysis regarding gene behavior in complex rearrangements and how this influences the patients' phenotype.

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Patient Consent: Informed consent was obtained from the patients' legal guardians for the publication of this case report and any accompanying clinical details and images.

Competing interests: The authors declare no competing interests and no kind of AI used.

Figure 1. Patient 1, female (a) and 2, a male (b-d). Craniofacial clinical features include epicanthic fold, antimongoloid slant of palpebral fissures, low-set and malformed auricles, high nasal bridge, long philtrum small mouth, micrognathia, short neck. Psychomotor retardation and Brachydactylic is evident.

Figure 2. Schematic graph of 4th chromosome, G-banded karyotype, and FISH karyotype of Patient 1. Karyotype FISH of Patient 2. The long branch for the duplication fragment is evident.

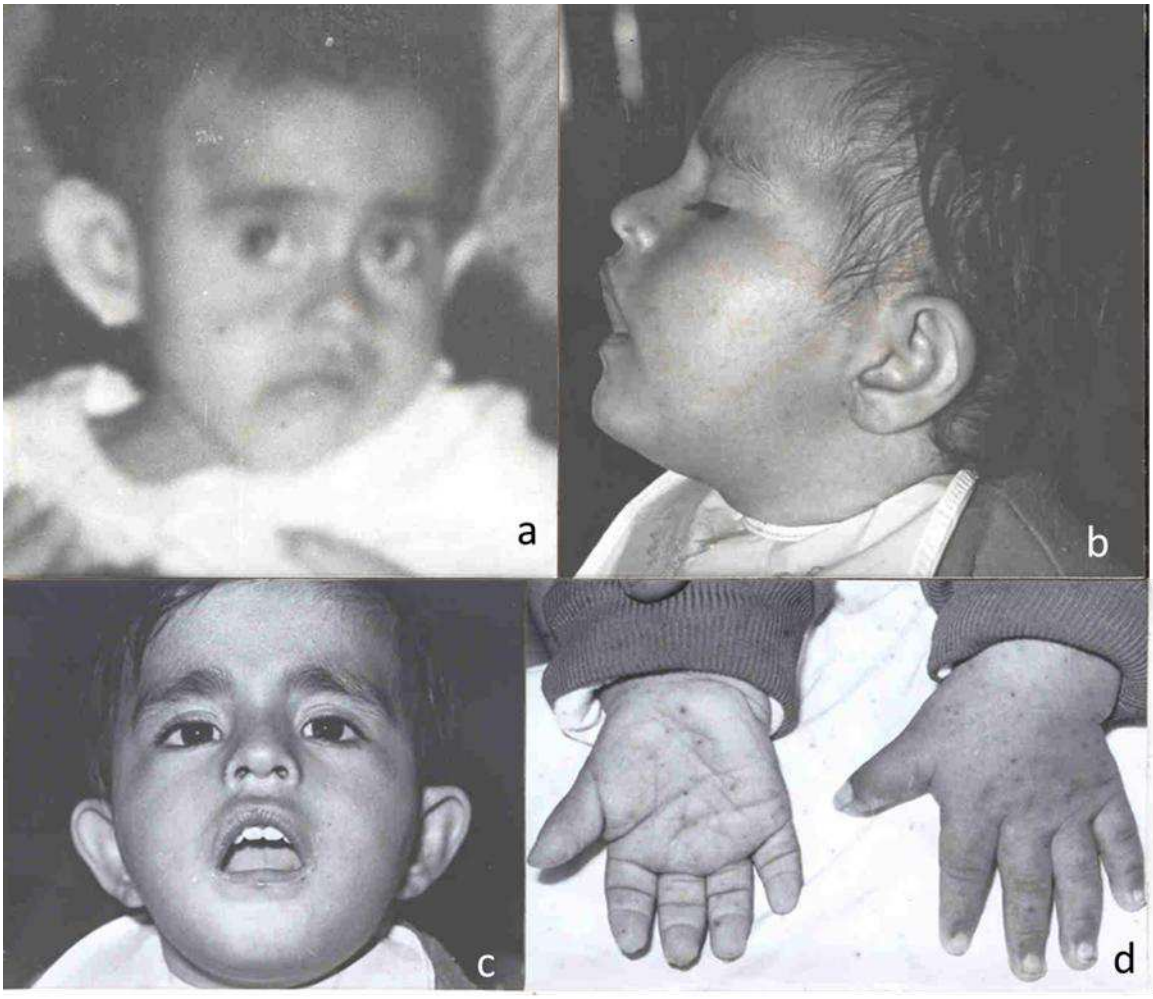


Figure 1

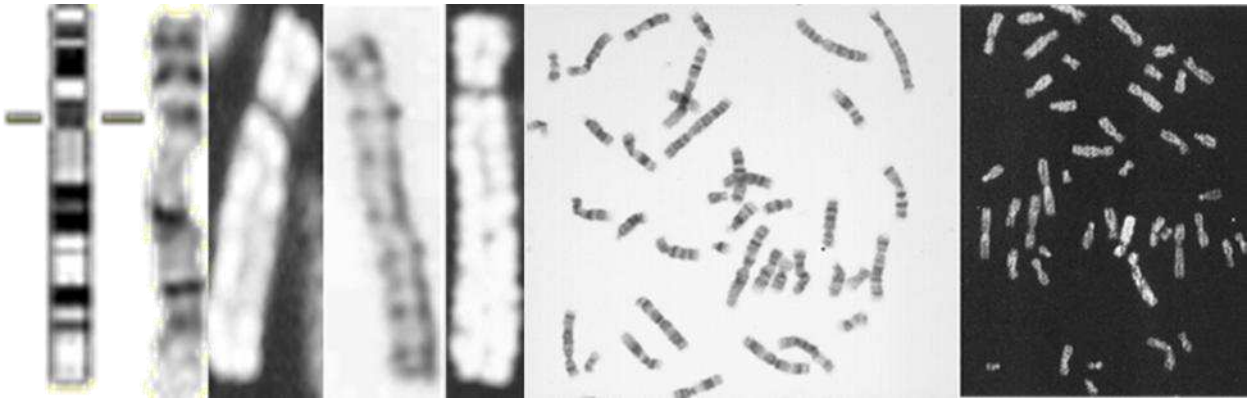


Figure 2

Supplementary information

Figure 3. Microsatellite electropherogram plot for one biomarker of chromosome 4, from the CODIS the FGA the allele 24 defining the maternal origin of the duplicated chromosome.

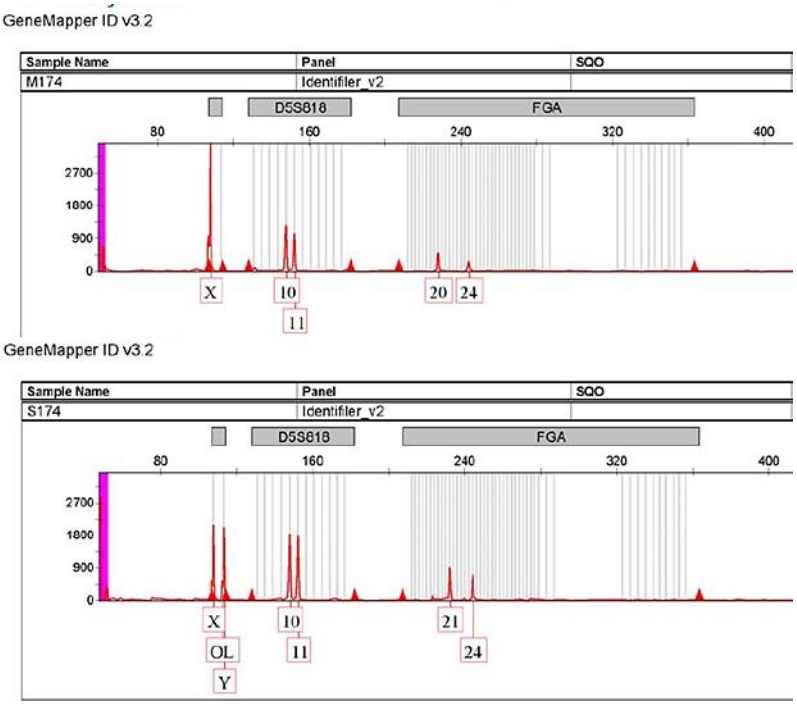


Figure 3

Supplementary Files

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