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Case Reports

A Neonate with Chromosome Xp21 Contiguous Gene Deletion Syndrome

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Abstract A 14-day-old male infant was admitted to our neonatal unit because of feeding difficulty, dehydration and weight loss. The initial analysis showed hyponatraemia and hyperkalaemia, increased plasma adrenocorticotropic hormone (ACTH) and increased plasma 17a-hydroxyprogesterone, decreased cortisol and plasma aldosterone and increased plasma 17a-hydroxyprogesterone, thereby making the 21-hydroxylase-deficient form of congenital adrenal hyperplasia likely. Cortisone acetate and fludrocortisone treatment corrected the electrolyte abnormalities and the patient improved. But the creatine kinase, lactate dehydrogenase, and triglyceride levels continuously increased. The urinary analysis revealed grossly increased levels of glycerol. At that point, chromosome Xp21 contiguous gene deletion syndrome was suspected. Further Multiplex Ligation-Dependent Probe Amplification analysis revealed both *DAX1* gene and all of the 79 exons of *DMD* gene were deleted in the boy's blood sample. Chromosome Microarray revealed an approximately 6.3 MB deletion on chromosome Xp21.3p21.1, including *DAX1, GK, DMD* and *IL1RAPL1* in the maternal sample. So the newborn was diagnosed as Xp21 contiguous gene deletion syndrome and his mother was a carrier.

Key words Adrenal hypoplasia congenita; Chromosome Xp21 contiguous gene syndrome; Glycerol kinase deficiency; Neonate

Introduction

Contiguous gene syndromes are disorders caused by deletions of genes that are adjacent to one another. One of them is chromosome Xp21 contiguous gene deletion syndrome, which is also named as complex glycerol kinase deficiency. It is caused by partial deletion of Xp21, which includes the genes responsible for adrenal hypoplasia congenita (AHC), glycerol kinase deficiency (GKD), Duchenne muscular dystrophy (DMD).[1-3] We describe a newborn infant with AHC and coincident hyperglyceroleamia leading to the diagnosis of chromosome Xp21 contiguous gene deletion and identification of DMD. We also describe the gene studies used to confirm the deletion in this infant.

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Case Report

A male infant conceived by assisted reproductive technology was born by vaginal delivery after a 40 weeks' uncomplicated pregnancy, to a 33-year-old woman. He was admitted to our department at age 14 days because of feeding difficulty, dehydration and a weight loss of 50 g from a birth weight of 2725 g. There was normal male external genitalia with slight hyperpigmentation noted. The examination of the cardiac system and lungs was normal with no abdominal organomegaly. Muscle tone was noted to be normal.

His plasma glucose was 4.3 mmol/L, his urine ketones was negative and blood gas analysis was normal. The initial electrolyte analysis showed hyponatremia (123 mmol/L) and hyperkalemia (7.8 mmol/L) without acid-base imbalance, prompting a working diagnosis of adrenal insufficiency. Subsequent investigation revealed increased plasma adrenocorticotropic hormone (ACTH) (115 pg/ml, normal 0-26 pg/ml), decreased cortisol (2.5 ug/dl, normal 5-25 ug/dl), decreased plasma aldosterone (58 pmol/L, normal 140-2500 pmol/L), and increased plasma 17a-hydroxyprogesterone (35.2 nmol/L, normal <30 nmol/L), thereby making the 21-hydroxylase-deficient form of congenital adrenal hyperplasia likely. Cortisone acetate and fludrocortisone treatment corrected the electrolyte abnormalities, and the patient improved. But both Multiplex Ligation-Dependent Probe Amplification (MLPA) and gene sequencing analysis for *CYP21A2* (gene for 21-hydroxylase) were normal. The ultrosonography showed small zones of adrenal cortex, and the laboratory investigation revealed elevated levels for creatine kinase (5082 U/L, normal 39-308 U/L), aspartate aminotransferase (155 U/L, normal 5-55 U/L) and lactate dehydrogenase (916 U/L, normal 225-600 U/L). Triglyceride levels are continuously increased (peak level 14.33 mmol/L, normal <2.26 mmol/L). The gas chromatography mass spectrometry for urinary analysis revealed grossly increased levels of glycerol. At that point, chromosome Xp21 contiguous gene deletion syndrome was suspected. But electromyography checks for upper and lower extremities were normal and a karyotype analysis revealed a normal male 46,XY status without noticeable deletions within the X chromosome. So we had to search for additional molecular studies to confirm.

Four milliliter sodium citrate anticoagulated blood were drawn from the infant and sent to KingMed (Hangzhou) gene company. Multiplex Ligation-Dependent Probe Amplification (MLPA) were used to analyse the *DAX1* (gene for X-linked AHC) and *DMD* genes, but unfortunately there were no *GK* (gene for GKD) probe available in this company. They found *DAX1* was deleted (shown in Figure 1A) and they also found all of the 79 exons of *DMD* were deleted (shown in Figure 1B and 1C). The deletions were suspected to be maternally inherited, so the maternal blood sample were sent for further analysis. Chromosome Microarray (CMA) were used by KingMed (Hangzhou) gene company for analysing the X chromosome. The result of maternal sample showed an approximately 6.3 MB deletion on chromosome Xp21.3p21.1, including *DAX1(300473), GK (300474), DMD(300377)* and *IL1RAPL1(300206)* (gene for intellectual disability) genes (showed in Figure 2). As to these gene results, the newborn was diagnosed as chromosome Xp21 contiguous gene deletion syndrome and his mother was a carrier. A low fat diet, mineralocorticoid and glucocorticoid replacement were advised for management. At the time of discharge on hospital day 28, his sodium was 135 mmol/L and potassium 3.9 mmol/L. His triglyceride level decreased to 8.1 mmol/L. His weight rose to 3060 g and the hyperpigmentation disappeared. We discussed with the parents about the genetic results, prognosis, present symptomatic treatments and future gene therapy for the disease. We gave them appropriate genetic counselling to plan for future reproductive options and suggested to do CMA for the baby. They refused because of economic issue and also because they thought there were enough genetic evidences for this disease, but they promised to be followed up closely. On follow-up, the patient continued to gain weight. Now the boy is six months old, he has normal electrolyte analysis and his triglyceride level deceases to 7.6 mmol/L but his creatine kinase increases to 11282 U/L. Up to now, he has no significantly reduced movement abilities.

Discussion

Chromosome Xp21 contiguous gene deletion syndrome was caused by partial deletion of Xp21 chromosome, genes from telomere to centromere: *IL1RAPL1, DAX1, GK, DMD.*[2] The symptoms depend on the size of election. As there are no specific dysmorphic features, the diagnosis is made on the basis of clinical and laboratory findings. Early patients are all males. Females are usually asymptomatic carriers, but they may have mild to moderate intellectual disability.

AHC is caused by a deletion of *DAX1* gene and characterised by the absence of permanent zones of adrenal cortex, which leads to deficiency of mineralo- and glucocorticoids.[4] The disorder usually starts during the first months of life. Symptoms are acute and include vomiting, failure to thrive, dehydration, hypoglycaemic seizures, and shock due to salt-wasting crisis. The deficiency of mineralocorticoids is more severe than the deficiency of other hormones and appears earlier, so salt-wasting symptoms are usually the first manifestation of the disease.[5]

Glycerol kinase (GK) catalyzes reaction of phosphorylation of glycerol to glycerol phosphate. Glycerol kinase deficiency (GKD) is caused by a deletion of *GK* gene. The symptoms of GKD most often appear between the age of 2 and 7.[6] Affected boys may present with episodes of vomiting, metabolic acidosis, ketotic hypoglycaemia,

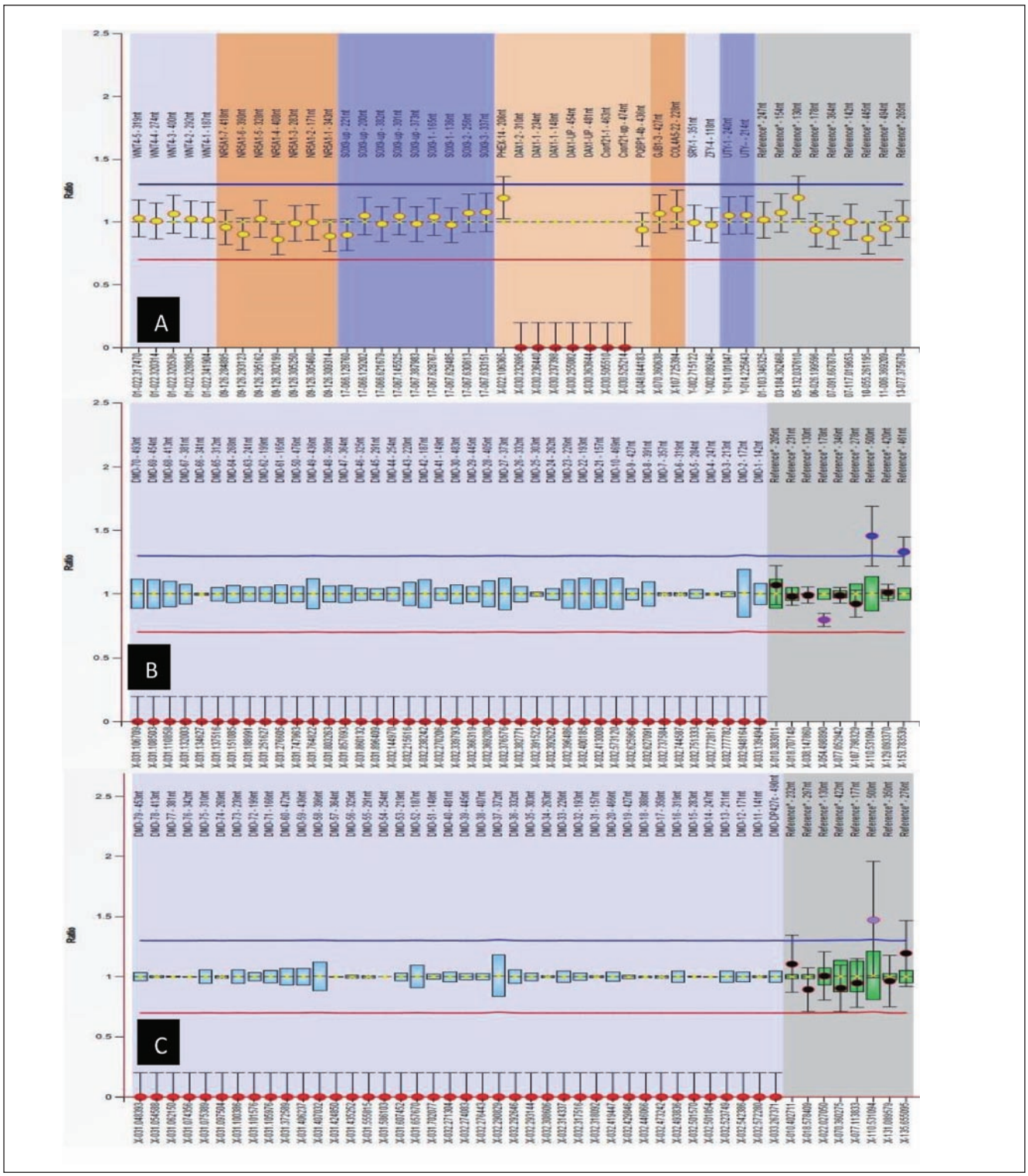

Figure 1 MLPA analysis for *DAX1* and *DMD*. *DAX1* gene was deleted in the neonate case (A). All of the 79 exons of *DMD* gene were deleted in the neonate case. (The first deleting parts of exons of *DMD* gene were showed in B and the second deleting parts of exons of *DMD* gene were showed in C).

progressive lethargy or unconsciousness. Usually, it is more severe in younger patients, but when it is associated with AHC, adrenal insufficiency may mimic the symptoms of GKD.[7] The most significant sign of GKD is highly increased level of glycerol in plasma and urine.[1,3] The estimation of glycerol is not a routine procedure. It is performed in individuals with very high level of "triacidoglyceroles" in plasma, as most widely used laboratory methods do not distinguish between glycerol and triacidoglyceroles.

DMD is caused by mutations in dystrophin gene, which is located on the Xp21.2 locus.[8] The absence of protein dystrophin causes progressive weakness of muscles. Creatine kinase (CK) level in serum is highly increased even at birth. It is correlated with degeneration of muscles. In electromyography (EMG), myopathic features are visible. But in our case, his normal EMG perhaps was related to his young age.

Patients with chromosome Xp21 contiguous gene deletion syndrome may suffer from intellectual disability.[1] It was discovered recently that a common cause of intellectual disability is the mutation of *IL1RAPL1* gene, which is located on chromosome Xp22.1-Xp21.3, next to *DMD* gene.[9] The majority of patients with deletion in this region have mental retardation regardless of any other disturbances.[10] In our case, the mother's molecular analysis showed *IL1RAPL1 gene* deletion in Xp21. It was highly suspected that the boy also had *IL1RAPL1* gene deletion, but unfortunately we did not get the result because of some social problems.

Chromosome Xp21 contiguous gene syndrome is newly recognised genetic syndrome. Physician should consider this syndrome in infants with adrenal insufficiency, increased levels of creatine phosphokinase and pseudohypertriglyceridaemia to be able to prevent and treat the metabolic complication. In order to accelerate the diagnostic workup and to allow genetic counselling of the affected families, a detailed analysis of each gene involved in the deletion is needed. The genetic diagnosis of these disorders could be technically difficult and requires different cytogenetic and molecular methods.

Declaration of Interest

We declare that we have no conflict of interests.

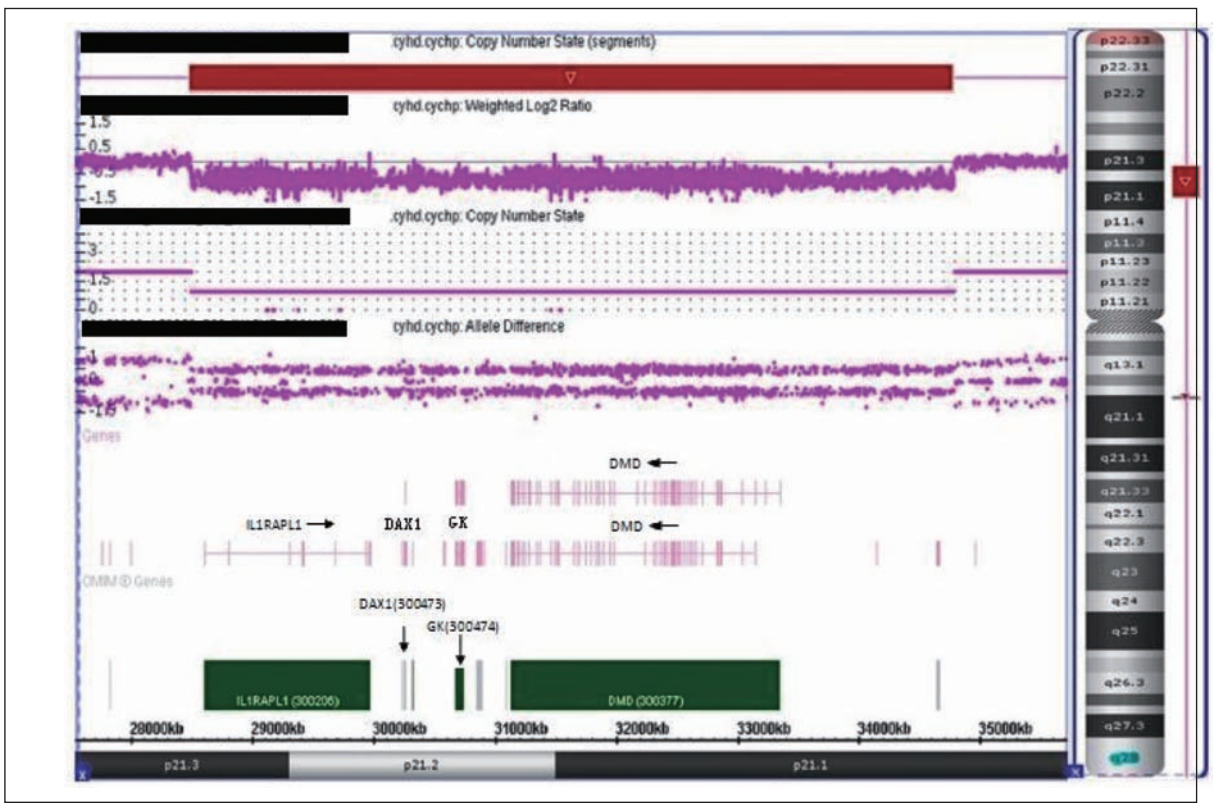

Figure 2 CMA analysis for maternal sample. Approximately 6.3 MB deletion on chromosome Xp21.3p21.1, including *IL1RAPL1, DAX1, GK, DMD* genes.

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