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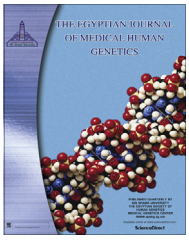

CASE REPORT

Primary ciliary dyskinesia: Kartagener syndrome in a family with a novel *DNAH5* gene mutation and variable phenotypes

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KEYWORDS

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Abstract *Background:* Primary ciliary dyskinesia is a genetically heterogeneous autosomal recessive disorder with variable clinical manifestations, including chronic rhinosinusitis, otitis media, bronchitis, pneumonia, bronchiectasis, situs inversus totalis, reduced fertility in female patients and male infertility. The condition occurs as a result of abnormal ciliary structure and function. It is presented in early life with an estimated incidence of approximately 1/16,000–20,000. About 50% of the affected patients have situs inversus totalis leading to Kartagener syndrome (MIM: 244400). So far more than 19 causative genes have been associated with primary ciliary dyskinesia.

Case report: Here we are presenting Kartagener syndrome in a consanguineous Kuwaiti family with a novel pathogenic *DNAH5* gene mutation; namely c.9864dupA; [p.Pro3289ThrfsStop52], which is predicted to result in protein truncation. In this family several homozygous individuals showed variable disease manifestations.

Conclusion: Molecular test helped in confirmation of the clinical diagnosis and in providing better management of the affected family members, which in turn could significantly improve overall quality of their life. Consequently, preimplantation genetic diagnosis, which is the most acceptable procedure in the Islamic countries, was offered to the heterozygous-carrier couple in order to prevent recurrence of the disease in their future generations.

1. Introduction

The name Kartagener syndrome (KS) came after the first author who in 1933 described the triad of situs inversus, chronic sinusitis and bronchiectasis as a distinct hereditary disorder [1]. KS (MIM: 244400) is a rare primary ciliary dyskinesia disease (PCD). PCD is a genetically heterogeneous class of disorders

Abbreviations: B–T shunt, Blalock–Taussig shunt; IVF, in vitro fertilization; KS, Kartagener syndrome; KMGC, Kuwait Medical Genetics Centre; PGD, preimplantation genetic diagnosis; S/P, systemic-to-pulmonary.

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known as ciliopathies, which are generally transmitted in an autosomal recessive manner. However, other modes of inheritance have been reported as well. These diseases have variable clinical manifestations including chronic rhinosinusitis, otitis media, bronchitis, pneumonia, bronchiectasis, situs inversus totalis (mirror image orientation of thoraco-abdominal organs), reduced fertility in female patients and male infertility. PCD occurs as a result of abnormal ciliary structure and function affecting many tissues and organs. The disorganized ciliary motions lead to impaired mucociliary clearance in the associated organs. These include the respiratory tract cilia, paranasal sinuses, Eustachian tube, middle ear, oviduct, spermaductus, flagella of sperm tail, brain and spinal cord ependyma [2]. Many syndromes are linked to ciliopathies including, PCD/KS syndrome, Bardet–Biedl syndrome, hydrocephalus, polycystic kidney disease, polycystic liver disease, nephrolithiasis, Meckel–Gruber syndrome and Joubert syndrome. About 50% of the affected patients have situs inversus totalis leading to KS. PCD is presented in early life with an estimated incidence of approximately 1/16,000–20,000 live births [3]. So far more than 19 causative genes have been associated with PCD: *DNAH5*, *DNAH11*, *DNAI1*, *DNAI2*, *RSPH9*, *RSPH4A*, *TXNDC3*, *KTU/PF13*, *LRRC50*, *CCDC39*, *CCDC40*, *CCDC103*, *HEATR2*, *LRRC6*, *DNAL1*, *DNAAF3*, *HYDIN*, *CCDC114*, *CCDC164*, *CCDC65*, *c21orf59*, *SPAG1*, *ZMYND10*, *RSPH1*, *ARMC4*, and *DYX1C1/DNAAF4*. Moreover, *RPGR*, and *OFD1* are additional genes involved in syndromic forms of PCD [4]. Mutations in *DNAH5* gene located on chromosome 5p, is responsible for KS. *DNAH5* encodes a protein associated with the outer dynein arm of the cilia, and highly similar to the Chlamydomonas γ-dynein heavy chain [5,6]. Variable phenotypes were observed with different mutations [6]. In this report we discuss a Kuwaiti family with several cases of KS carrying a novel homozygous *DNAH5* gene mutation, and presenting different phenotypes.

1.1. Family data

The family presented here is a highly consanguineous Kuwaiti family, in which double first cousin marriages have been frequently practiced. In this family 5 cases of KS of variable severity were observed.

1.2. Patient 1

This is the proband, a 27 year old female, who was referred by the IVF unit at the Maternity hospital, for genetic counseling and testing in preparation for preimplantation genetic diagnosis (PGD). She is the first cousin of her husband, had two children with congenital heart disease (Fig. 1). The first child was a boy, diagnosed antenatally with situs inversus totalis. He was born at full term, after an uncomplicated pregnancy, with complex cyanotic congenital heart disease. His medical report revealed right atrial isomerism with dextrocardia, complete atrioventricular septal defect with pulmonary atresia, supracardiac total anomalous pulmonary venous connection (TAPVC) to left sided superior caval vein (right sided inferior caval vein), and with S/P left sided BT shunt. He died postoperatively at the age of 6 weeks. Two years later she had her second child (patient 2), a girl, born at full term with situs inversus totalis (dextrocardia), but with no complication. She is currently 3 years old and doing well.

1.3. Patient 3

Proband's mother was aged 56 years. Her parents were double first cousins. She was also diagnosed with situs inversus totalis with no complications throughout her life. She gave a history of chronic sinusitis since childhood, requiring drainage and myringotomy. Her mother had also situs inversus totalis, but with a healthy life and no medical complications. However, she died at the age of 57 years from stroke.

1.4. Patient 4

She was the first cousin of the proband, seen at the age of 19 years. Her parents were also consanguineous (Fig. 1). She had no cardiac abnormalities. However, she gave a history of recurrent middle ear infections and chronic sinusitis that was treated several times with steroids. Her maxillary sinuses were drained at the age of 12 years. She had myringotomy, for three times, in both ears with pressure equalization tubes. Her latest CT scan showed chronic inflammatory changes of frontal and maxillary sinuses along with nasal septum deviation, hypertrophic turbinates and nasal polyps. An endoscopic sinus surgery with image guidance was planned for her. She had two normal elder sisters and a younger brother. Additionally, she had another brother who died at the age of 8 months due to complex cyanotic congenital heart disease.

2. Methods

The written informed consent was obtained from the proband and her adult relatives for blood collection and molecular testing. The process involved 19 family members approaching KMGC and requesting predictive gene testing. The genomic DNA was extracted from the peripheral blood for defining the carrier status of the involved subjects. Following PCR amplification of the DNA, primary sequence analysis of the entire coding region of the commonly involved *DNAH5* gene was performed for the affected child (patient 2) and her grandmother (patient 3). For other relatives targeted sequencing of both familial mutation and alteration was performed separately, by utilizing the following forward and reverse primers for each exon respectively: Exon 58 Primers [F-5′-TGCATTTTCAGCTGGATGTT-3′, and R′-5′GTCTGCCTCTTAAGCCCTAA-3′]; Exon 14 primers [F-5′-GGGGCTGACATTGATATGAT-3′ and R-5′-GAAGAGGGGTTCCCATGATT-3′].

3. Result

Patients 2, 3 and 4 were found to be homozygous carrier for the c.9864dupA; [p.Pro3289ThrfsStop52], in exon 58 of *DNH5* gene (Fig. 2). This is a pathogenic mutation predicted to result in protein truncation, and describing the associated clinical features. Additionally, all of them carried a homozygous alteration in exon 14 of *DNAH5* gene. This sequence variant is defined as c.1853G > A, and predicted to result in the amino acid substitution p.Arg618Gln. This sequence variant

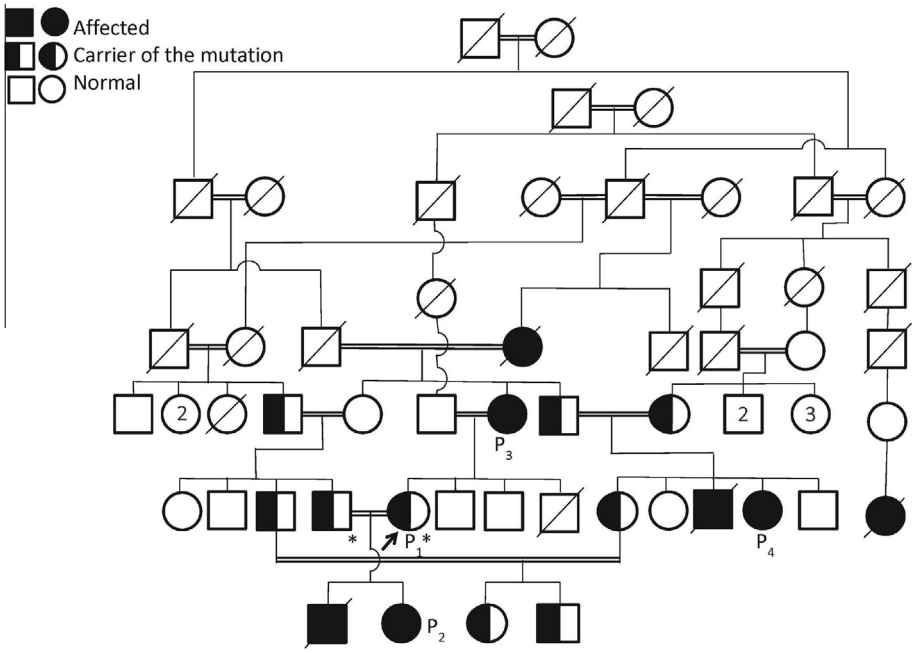

Figure 1 Family pedigree. The proband (P_1) is indicated by an arrow. The couple embarking on PGD is indicated by the star sign (*). P_1: patient 1, P_2: patient 2, P_3: patient 3, P_4: patient 4.

is not predicted to abrogate known splice sites or disrupt splicing. However, the mutation taster program (http://www.mutationtaster.or) predicts the c.1853G > A; [p.Arg618Gln] to be a disease causing variant.

Moreover, 9 other relatives were found heterozygous carriers for the same pathogenic mutation in exon 58 as well as for the sequence variant found in exon 14 of the same gene. These were parents of patient 2 (patient 1 and her husband), grandfather of patient 2, parents of patient 4, elder sister of patient 4 that was married to her first cousin, who was a carrier too, and their two children (Fig. 1).

4. Discussion

KS is one of the PCD diseases that are inherited in an autosomal recessive fashion. In Kuwait, similar to other Arab countries, the prevalence of consanguineous marriages is high and it reached 54.3% [7]. Consequently, this leads to an increased incidence of autosomal recessive disorders some of which are rare and lethal [8,9]. In this report, pedigree analysis revealed that the concerned family had practiced consanguinity over many generations, and with many first cousin couples (Fig. 1). Moreover, parents of patient 2 were first cousins, her paternal grandparents were double first cousins, while the maternal grandparents were second cousins. There is a history of other affected infants who died of similar heart conditions, but we could not clarify this, as medical reports were no longer available. Clinical manifestations varied between affected individuals in this family; some had situs inversus totalis with/or without respiratory tract disorders, one had only respiratory tract problems and the closely related dead boy had heterotaxy (lethal complex heart disease with right atrial isomerism). In PCD, situs inversus was proposed to occur as a random phenomenon due to loss of nodal ciliary function, which is important for organ orientation during embryogenesis [10]. Intra-familial phenotypic variability had been observed in the literature [10,11]. Heterotaxy was detected in 6.3% of individuals with PCD, and most of those carried cardiovascular abnormalities. Moreover, it was frequently associated with mutations in *DNAI1* and *DNAH5* genes [11]. However, no genotype phenotype correlation had been detected in a cohort of patients selected from different European and North American families, who were tested for *DNAH5* gene mutation in a study by Hornef et al. [12]. On the contrary, screening of patients from Amish and Mennonite communities revealed phenotypic variability in homozygous carriers of the *DNAH5* gene with 4348C > T founder mutation [13]. Therefore, we are not sure whether the phenotypic variability in our family is associated with the mutation position in the *DNAH5* gene, or is simply due to the randomization of left–right asymmetry. Hence genetic screening is a valuable approach for assisting the diagnosis in patients with these types of anomalies and should be applied in the clinical setting.

We have identified a disease-causing mutation in exon 58 of the *DNAH5* gene; namely c.9864dupA; [p.Pro3289Thrfs-Stop52] in a high-risk family. This pathogenic mutation is novel and occurred in a homozygous state in the 3 available affected individuals, and in a heterozygous state in 9 closely related members of their family. Another variant was also found in exon 14; c.1853G > A, in the same individuals; which was in a homozygous state in the 3 affected members and in a heterozygous state in the same 9 carriers of the pathogenic exon 58; c.9864dupA mutation. Since we are not sure of the pathogenicity of the latest, this will be screened for in the embryos during the PGD processes. Molecular test helped in confirmation of the clinical diagnosis in the affected members, and in planning the future reproductive health strategy for the heterozygous couples from this family. Patient 1 is currently under preparation for PGD using in vitro

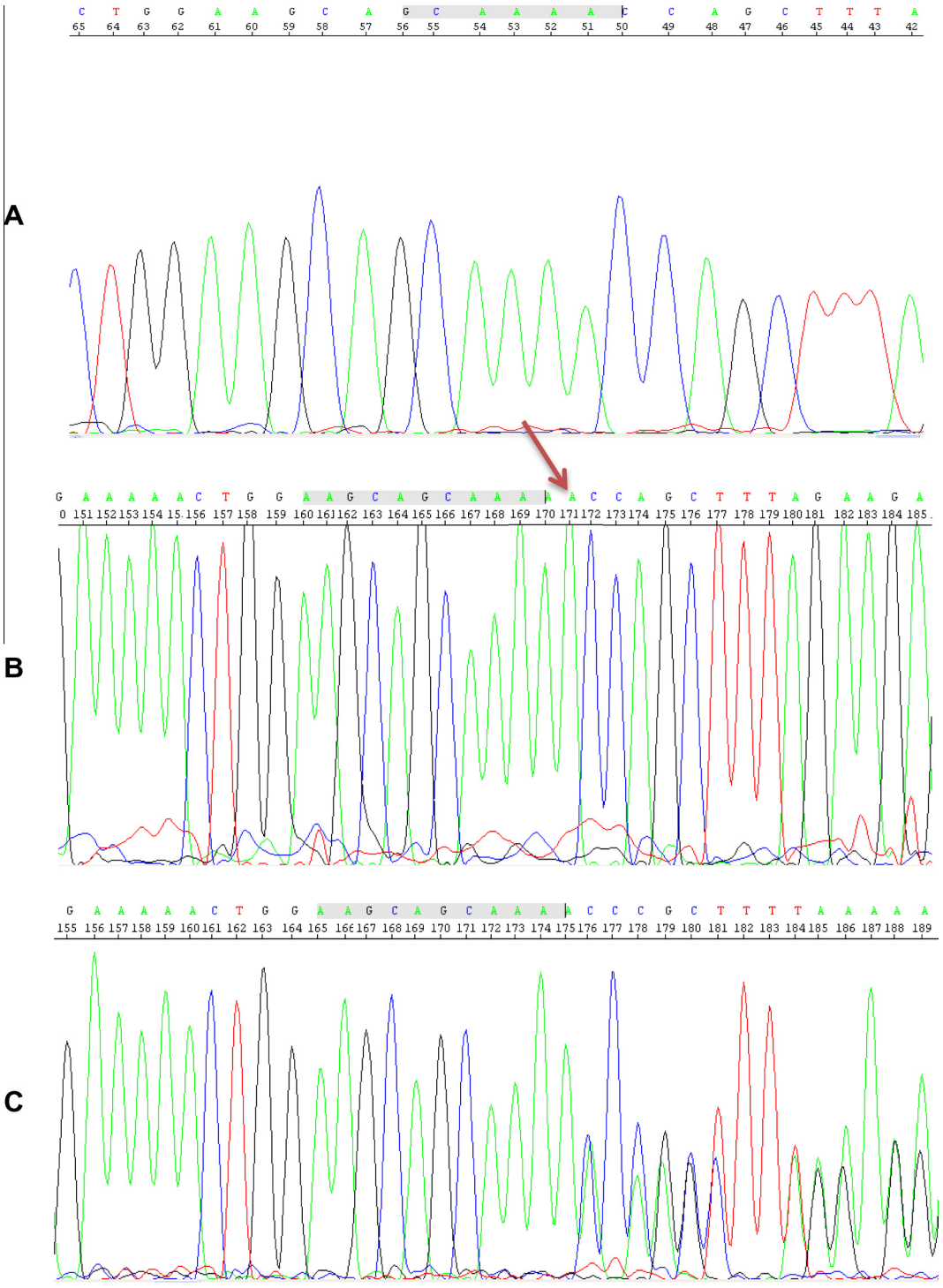

Figure 2 Electropherogram of the homozygous mutation c.9864dupA (arrow), exon 58 of *DNAH5* gene found in patient 2 and her relatives. (A) Wild type. (B) Homozygous carrier. (C) Heterozygous carrier.

fertilization, in order to prevent recurring of the disorder in the next pregnancy.

5. Conclusions

In the Arab communities the rate of autosomal recessive diseases is high due frequently practiced consanguineous marriages. A large number of these diseases are rare and devastating. Therefore, efforts should be directed toward planning intensive educational programs to increase the awareness of the public about the possible outcome risks of consanguineous marriages. Moreover, special emphasis should be given to educate the health care professionals who are involved in providing the premarital genetic services, in order to recognize high-risk families with varieties of debilitating disorders, to better manage these cases and to refer the selected

couples to the genetics clinics. Whereas clinical geneticists should be trained for providing genetic counseling and screening, describing the reproduction options to couples at risk, and for long term family health care management for the benefit of their new generations. Finally, PGD procedure is the best prevention option to avoid the birth of children with genetic disorders in families who do not want to terminate the pregnancy for any reason. However, it remains a financial problem for the unfortunate low income families.

Note

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