Intrafamilial Phenotypic Variability in Two Siblings with Primary Ciliary Dyskinesia Due to Homozygous Loss of Function Mutation in the *CCDC151* Gene

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Primary ciliary dyskinesia (PCD) is a group of rare clinically and genetically heterogeneous autosomal recessive diseases that collectively result in structural and functional impairment of motile cilia. These respiratory ciliopathies, with reduced mucociliary clearance of the airways, may manifest in early childhood and affect multiple body systems. Manifesting in early childhood, PCD affects multiple body systems including the sinuses, ears, respiratory tract, and reproductive systems and may result in diverse clinical manifestations including recurrent pneumonia, recurrent otitis media, sinusitis, chronic rhinorrhea, infertility, and situs inversus. Since the clinical manifestations of PCD overlap with many common pediatric morbidities (otitis media, pneumonia, chronic rhinitis) diagnosis is often delayed and requires a high index of suspicion [1].

Diagnosis of PCD is challenging and reflects the lack of universal consensus [1,2]. Traditionally, at clinical suspicion of PCD, the combination of extremely low levels of nasal nitric oxide and abnormal ciliary ultrastructural analysis strongly support the diagnosis of PCD. Recently these symptoms served as confirmatory diagnostic assessments. Ciliary ultrastructural examination is obtained by bronchoscopy (lower respiratory epithelium) or nasal brush of the inferior turbinate. The specimen collected is examined by transmission electron microscopy (TEM) to identify abnormal cross section morphology of motile cilium. In addition, high speed video analysis, including ciliary beat frequency and beat pattern analysis, may be used as part of the diagnostic workup of patients suspected of having PCD [2]. Nevertheless, approximately 30% of PCD cases have normal ciliary ultrastructure and therefore definite diagnosis relies on genetic studies [2]. Diagnosis could be further confirmed by genetic analysis and identification of a genetic mutation consistent with PCD pathology.

To date, pathogenic variants in more than 30 genes have been shown to cause PCD, making its precise genetic diagnosis a true challenge for the clinician [1,2]. In this case study, we report on two sisters of Bedouin origin with PCD caused by a homozygous mutation in the *CCDC151* gene. This gene was recently recognized to result in PCD by impairing the formation of normal ciliary outer dynein arms [3]. To the best of our knowledge, these sisters are the first PCD reported patients in Israel caused by *CCDC151* gene mutations.

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PATIENT DESCRIPTION

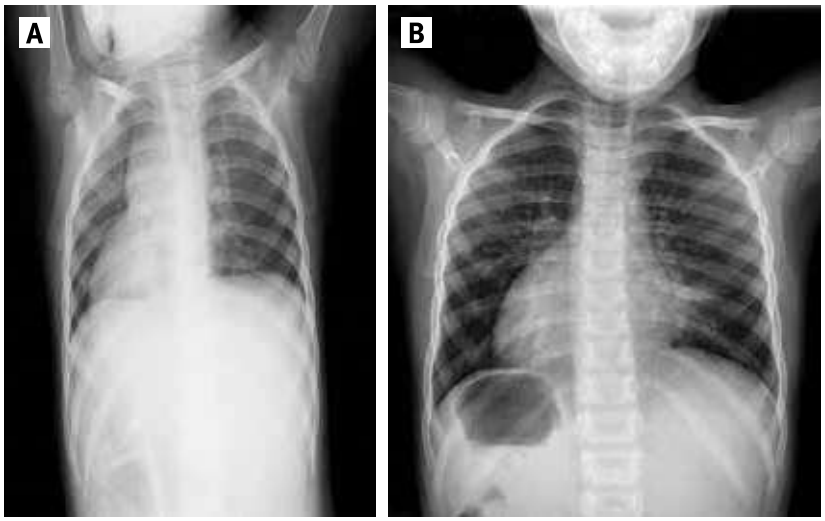
PATIENT 1

This female, 6 years of age, was the first offspring of healthy first degree cousins of Bedouin descent. Her perinatal period was unremarkable. She initially presented in infancy with chronic rhinitis and cough and recurrent purulent otitis media. As a result of recurrent purulent otitis media, she had undergone several ventilation tube insertions in both ears, presented with conductive hearing loss, and used hearing aids. On her last appointment at the age of 6 years, her physical examination revealed a well-nourished girl with normal development and growth (weight and height were at 10th and 25th percentiles, respectively), clear lungs, and right-sided heart sounds. Chest radiography and echocardiographic examination identified that the patient had situs inversus totalis without any structural or valvular heart defects [Figure 1A]. Interestingly, her patient file and history did not record any episode of lobar pneumonia or respiratory infection that required hospital admission and her situs inversus was unrecognized.

PATIENT 2

This 4-year-old girl, was the young sister of patient 1. She was born at term after a normal unremarkable pregnancy and delivery. Immediately after birth she experienced a significant desaturation episode accompanied with tachypnea and respiratory distress. A chest X-ray was performed

Figure 1. [A] Chest X-ray of a patient 1 at the age of 6 years showing dextrocardia but no lung infiltrates. **[B]** Chest radiograph of patient 2 at the age of 4 years displaying dextrocardia over-inflation, atelectasis and chronic changes in her left lung



and revealed bilateral infiltrates and situs inversus. She was discharged home after 20 days in the neonatal intensive care unit with home oxygen supplementation on demand. Since infancy she had presented with a chronic wet cough and rhinorrhea, recurrent pneumonia, and recurrent otitis media. She had undergone ventilation tubes insertion due to recurrent ear infections and therefore she gradually developed conductive hearing loss. In addition, her growth was retarded with both weight and height at 3rd and 1st percentiles, respectively. At the age of 9 months, nasal brush was performed showing immotile cilia by light microscopy and absence of outer dynein arms in 86% of the cilia by TEM examination, which is consistent with the diagnosis of PCD. Despite intensive treatment including inhaled hypertonic saline, daily chest physiotherapy, and frequent antibiotic treatment, a chest radiograph showed, in addition to known dextrocardia, chronic lung infiltrates and left atelectasis, and sputum cultures grew multiple bacteria including *Pseudomonas aeruginosa.*

Following the presumed diagnosis of PCD in patient 2, a diagnostic genetic panel of primary ciliary dyskinesia was performed. The panel included 36 disease causing genes that were evaluated for sequence changes and exonic deletions/duplications (Invitae Genetic Laboratories San Francisco, CA, USA). The analysis identified both sisters to be homozygous to the pathogenic variant c.925G>T in the *CCDC151* gene that results in a premature protein truncation (p.Glu309*), which was previously reported in several PCD patients [3,4]. As expected both parents were heterozygous carriers.

COMMENT

CCDC15 is a coiled coil protein composed of 595 amino acids encoded by the *CCDC151* gene. This axonemal protein plays a pivotal role in the assembly of outer dynein arms in motile cilia cells in humans. Truncating mutations in this gene were recently shown to result in typical PCD phenotype with laterality defects [3].

To the best of our knowledge, only three other reports describing a total of seven patients presenting with PCD due to mutations in *CCDC151* gene were published [3-5]. Interestingly, only three homozygous mutations were recognized, all of which are nonsense mutations predicting early truncation of the protein. Of interest, one mutation c. 925G>T recurred in five patients all of whom from Arab ancestry, four of them Bedouin and one Egyptian [3,4]. The two patients described here are of Israeli Arab Bedouin origin and they also harbor the same homozygous mutation at c.925G>T suggesting this mutation should be regarded as a pan-Arab founder mutation. Notably, our study highlights the intrafamilial clinical variability in *CCDC151* mutations where the older sister manifested situs inversus and recurrent ear infections with already irreversible hearing loss but absent pulmonary involvement, while the younger sister presented immediately after birth with respiratory distress and later developed chronic lung disease and failure to thrive as well as situs inversus and middle ear infections. To our knowledge, intra-familial variability, which is known in other PCD causing genes, was not reported so far in *CCDC151*. This remarkable variability may be explained by the effect of various modifier genes that interact with CCDC151 protein as well as environmental factors such as increased or decreased exposure to viral or bacterial infections.

The introduction in recent years of next generation sequencing technologies into clinical practice has enabled successful resolution of several undiagnosed genetic cases in various clinical fields. Relevant to this report, an extensive PCD gene panel proved useful in the diagnosis of the two patients described. Based on the availability and rapid time scale of these panels, as well as their added contribution to future identification of carrier individuals in the broad family and the opportunity to offer prenatal diagnosis, we suggest to carry on with PCD extensive gene panels once the diagnosis is strongly suspected.

CONCLUSIONS

PCD should be suspected in any child with neonatal unexplained respiratory pathology, chronic rhinorrhea, recurrent infections of the ears, and/or chronic wet cough especially if associated with situs inversus. The growing use of specific large scale PCD gene panels offers clinicians an advanced, rapid, and non-invasive diagnostic tool.

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Capsule

Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus-2

SARS-CoV-2 is thought to have originated in bats; however, the intermediate animal sources of the virus were suspected to be pangolins or snakes, but whether other animals are involves in the pandemic is unknown. **Shi** et al. investigated the susceptibility of ferrets and animals in close contact with humans to SARS-CoV-2. The authors found that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but ferrets and cats are permissive to infection. SARS-COV-2 RNA was isolated from infected dog stool, but no live infective virus was found. Ferrets and cats have only two amino acids difference in the ACE2 receptor compared to humans, so they can be an acceptable model for experiments. The authors found experimentally that cats are susceptible to airborne infection. This study provides important insights into the animal models for SARS-CoV-2 and animal management for COVID-19 control.

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Capsule

The perception of complex scents

It is generally assumed that olfactory receptors faithfully report information to the brain in the form of a linear, additive code. However, under realistic conditions, the olfactory system handles a far more complex input, usually mixtures of odors. **Xu** et al. found that when we smell scents, the nasal olfactory sensory neurons relay a more complex pattern of signals to the brain than previously thought. The responses of individual neurons within the peripheral olfactory epithelium were either amplified or attenuated by the presence of other odors, which could explain the common perception of one odor in a mixture dominating over others. This effect occurs within the peripheral sensory organ's receptors and not within the brain.

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Capsule

Ironing out the details of mucosal healing

Anemia is a frequent complication of disorders such as inflammatory bowel disease, occurring in part as a result of increased bleeding into the intestine. **Bessman** and colleagues showed that the peptide hormone hepcidin, which regulates systemic iron homeostasis, is required for intestinal repair in a mouse model of inflammatory bowel disease. This effect was independent of hepatocyte-produced hepcidin and systemic iron levels. Instead, production of hepcidin by conventional dendritic cells was necessary and sufficient to promote local iron sequestration by macrophages, which in turn modulated the makeup of the gut microbiota to one with a more beneficial distribution of species.

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"A true friend is the greatest of all blessings, and that which we take the least care of all to acquire"

Francois de La Rochefoucauld (François VI, Duc de La Rochefoucauld, Prince de Marcillac) (1613–1680), noted French author of maxims and memoirs