Primary Ciliary Dyskinesia as a common cause of bronchiectasis in the Canadian Inuit population

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Abstract

with other laboratory and clinical investigations. Early and accurate diagnosis of inherited conditions generally leads to better medical care for patients and their families, with improved knowledge of the natural history of the condition and early intervention. It is therefore essential that equitable access to such testing is established for indigenous and isolated populations, in order to further narrow the health disparity gap. Although supported by funding from a few sources, this study signals a success for the Silent Genomes Project, with one of the cases having been identified by whole genome sequencing within that project, after negative whole exome sequencing. Furthermore the study has potential life-changing clinical consequences and provides starting points for possible interventions for respiratory medicine in the Inuit population. These include increased awareness of the possibility of PCD in patients presenting with neonatal respiratory distress, bronchiectasis or otitis media leading to early intervention; and in conjunction with Inuit organizations and public health officials, targeted analysis of the *DNAH11* variant in the population with the possible introduction of newborn screening for PCD.

Editorial on: Hunter-Schouela J et al. First report of Primary Ciliary Dyskinesia caused by a shared *DNAH11* allele in Canadian Inuit

Primary Ciliary Dyskinesia as a common cause of bronchiectasis in the Canadian Inuit population

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Increased rates of upper and lower respiratory tract illness and otitis media in Inuit children have been known for a long time.[1] An increased prevalence of non-CF bronchiectasis later in life has also been reported.[2]The reasons for this are not fully understood and are likely to be multifactorial, however the findings of Hunter-Schouela *et al.*[3] in this issue of the journal may provide a missing link. They report a novel, pathogenic, possible founder DNA variant causing Primary Ciliary Dyskinesia (PCD) in Inuit patients from different geographical areas of the Nunavut (Qikiqtaaluk region, Baffin Island) and Nunavik (Northern Qebec) regions in Canada, which may well be a contributing factor to the finding of increased bronchiectasis in this population. The DNA variant, c.4095+2C>A in the*DNAH11* gene, was found in 7 Inuit patients with PCD, from four families, by genetic testing in three different Canadian centers. All affected individuals were homozygous for the variant and although its effect has not yet been confirmed at the RNA level, the variant is not present in the gnomAD database (www.gnomad.org), nor has it previously been reported and it is strongly predicted to have an effect on splicing.

Previous estimates of bronchiectasis in Inuit children in the Qikiqtaaluk Nunavut region are as high as 1/500[2] and based on the finding of five affected PCD patients in an approximate population size of 16,000 Inuits,

Hunter-Schouela *et al.* have roughly estimated that the *DNAH11* variant may have a carrier frequency as high as 1/19 individuals. The age at genetic diagnosis in the patients varied from 4 to 59 years, partly due to late clinical diagnosis, but also due to varying severity. Four patients had laterality defects, whereas the other 3 had situs solitus. Other clinical findings were typical of PCD, including neonatal respiratory distress, bronchiectasis, chronic atelectasis, chronic rhinitis and chronic otitis media. *DNAH11* encodes one member of the axonemal dynein heavy chain protein family[4] that contributes to the assembly of respiratory cilia. It is also one of the causes of PCD that is not well diagnosed by routine cilia diagnostics, such as standard transmission electron microscopy (TEM). Hence the respiratory cilia appeared to be normal in 5 of the patients in this study for whom this was investigated, which delayed the recognition of PCD.

Although PCD is a rare disease, recent calculations predict that it is more common than previously assumed, with the minimum global prevalence now estimated to be at least 1/7550[5]. More than 50 genes have been identified as being causative of PCD which is characterized by allelic as well as genetic heterogeneity with many different pathogenic variants described in each of the genes.*DNAH11* is one of, if not the most common cause of PCD in world populations[5].

Although much of the research on PCD and most diagnostic tests have been performed on North American and European patients, this is not the first study highlighting that the prevalence of PCD may be higher in non-European populations. Hannah *et al*[5].highlighted from their study of pathogenic PCD variants in the gnomAD database, that the prevalence of carrying two disease-causing alleles in a PCD gene is generally higher in individuals of African descent than in most other populations. Their data suggested that patients of non-European ancestry might specifically be in need of PCD workup. Founder variants in other PCD genes have been previously reported in different populations[7,8,9,10,11]. In many cases these findings have enabled a more targeted approach to genetic testing, with analysis of the founder variant being the first line of testing before going on to a more expensive and time-consuming next-generation gene panel, whole exome or whole genome sequencing to screen all known PCD genes[12].

Genomic medicine and genetic testing have historically been relatively inaccessible to indigenous and isolated populations[13], for manifold reasons including the lack of access to genetic services and diagnostic laboratories, as well as the expense of genetic testing. Fortunately this is changing, with a steady reduction in the cost of diagnostics and an appreciation of the clinical utility of "mainstreaming" genomics, bringing genetic testing in line with other laboratory and clinical investigations. Early and accurate diagnosis of inherited conditions generally leads to better medical care for patients and their families, with improved knowledge of the natural history of the condition and early intervention. It is therefore essential that equitable access to such testing is established for indigenous and isolated populations, in order to further narrow the health disparity gap. Although supported by funding from a few sources, this study signals a success for the Silent Genomes Project, with one of the cases having been identified by whole genome sequencing within that project, after negative whole exome sequencing. Furthermore the study has potential life-changing clinical consequences and provides starting points for possible interventions for respiratory medicine in the Inuit population. These include increased awareness of the possibility of PCD in patients presenting with neonatal respiratory distress, bronchiectasis or otitis media leading to early intervention; and in conjunction with Inuit organizations and public health officials, targeted analysis of the *DNAH11* variant in the population with the possible introduction of newborn screening for PCD.

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