One person can make a difference: identification of people with a rare genetic lung disease

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Shareable abstract (@ERSpublications)
To improve access to care for rare conditions in resource-restricted regions, a concerted effort to establish centres of excellence and training of local physicians is needed https://bit.ly/3ZTBvaj

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Primary ciliary dyskinesia (PCD) is a rare, mostly autosomal recessive condition that affects the function of motile cilia in the airways, sinuses, middle ears and reproductive organs. Patients often present early in life with respiratory distress in the neonate and later with recurrent sinopulmonary infections that can progress to end-stage lung disease. Almost two decades have passed since finding the first gene associated with PCD [1, 2]. Now with >50 genes associated with PCD, the task of identifying patients continues to be complex, requiring advanced diagnostic tools and expertise that are not always available in low-income countries. In such settings, the task falls on the shoulders of dedicated and resourceful individuals, and a larger PCD community that is willing to lend a hand in the process.

PCD diagnostic criteria have been set forth by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [3]. Diagnosis requires screening patients for clinical criteria, followed by either transmission electron microscopy (TEM) or genetic testing, as well as performing nasal nitric oxide (nNO) measurement. These tools typically require a centre with technical expertise in performing cilia TEM and analysing the ultrastructure changes, as well as experience performing genetic analysis (whether using a commercial panel, in-house panel or whole-exome sequencing). In addition to the expertise required, these tests are expensive and burdensome for a medical system or patients in resource-restricted regions.

In this issue of *ERJ Open Research*, Rumman *et al.* [4] describe a cohort of patients with PCD in Palestine, an area with limited resources compounded by decades-long conflict and restrictions. The Palestinian population in the West Bank area cared for by N. Rumman's group, who have been living in this narrow region for many generations, are closely related and some with tribal origins. As a result, there is a higher incidence of autosomal recessive disorders in the region, sometimes restricted to specific villages [5–7]. An interesting finding is the frequency of different gene variants (at least seven) and the unique founder variants within this community. The data generated from this voluminous, demanding work adds to the description of PCD from nearby regions in the Middle East and can possibly be used to trace human migration across the region [8–11], for those interested in human history.

A special aspect of this study, however, is the tremendous work that was performed by a single pulmonologist, without a formal PCD centre and without the local resources for complex diagnostic testing. The first author (and a group of local physicians) screened 464 individuals with sinopulmonary disease suggestive of PCD and performed nNO measurement on 350 individuals. With the help of colleagues in the UK, samples were analysed by TEM from 183 patients and of those, 82 had genetic testing. Using this cohort, 68 out of 464 individuals had a confirmed TEM or genetic diagnosis of PCD, based on stringent criteria. It is notable that seven variants were identified at a high frequency, suggesting a shared ancestorial origin. This includes variants in *CCDC39*, *CCNO*, *DNAAF4*, *DNAAF11*, *DRC1*,

RSPH9 and *DNAH11*. Three of these variants were reported in a different cohort of Palestinians [8, 12–15]. Three novel candidate genes were also identified. To put this feat of work in perspective, a large PCD referral centre in the USA screens about 40–100 individuals for PCD per year.

Due to the high frequency of some alleles within specific families, likely due to founder mutations, the authors were able to use allele-specific PCR against mutations in *CCDC39* and *DNAAF11* for diagnosis. This option may allow a cheaper and more accessible alternative to commercial panels.

It is also noteworthy that despite the relatively high number of patients that were identified in this cohort, it is likely that many individuals with PCD may not have been identified. Genetic and TEM testing was highly selective and did not include patients with PCD like symptoms whose nNO measurements were >77 nL·min^{-1} (the cut-off established by the ATS and ERS guidelines). Though this cut off is a good starting point, it is well established that many patients with PCD due to PCD genes (*e.g. RSPH1*, *GAS8*, *RPGR*, *CCNO*, *CCDC103*, *CFAP221*, *DNAH9*, *FOXJ1*, *GAS2L2*, *LRRC56*, *NEK10*, *SPEF2*, *STK36*, *HYDIN* or *TTC12*) have nNO values >77 nL·min^{-1}. This information suggests that the burden of disease may be even higher within the Palestinian population.

To improve the health of the people within the region, a consorted effort to establish centres of excellence in resource-restricted areas such as Palestine will be required. Such a response can improve the diagnosis and treatment of PCD, and other rare conditions such as genetic immunodeficiency diseases that have features overlapping PCD. The collaboration between the authors of this paper is one example of how this effort can be supported, starting by training talented individuals and providing the diagnostic support (locally or at a centralised centre overseas).

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