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Letter to the Editor



LETTER TO THE EDITOR

# Utilizing artificial intelligence and next-generation sequencing to facilitate the diagnosis of rare diseases

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To the Editor,

Worldwide there were more than 6000 rare diseases affecting 3.5%–5.9% of all people in the year 2020 [1]. Another study suggested that approximately 1.6% of patients who visit a primary care physician have a rare disease [2]. Thus, diagnosis of rare diseases is vital not only in specialized medical centres, but also in general practice. Next-generation sequencing (NGS) is the gold standard for diagnosing rare diseases, as in recent years it has become more affordable and accessible. Yet, the entire process of sample preparation, sequencing and data analysis can take several months, especially when the analysis is untargeted. Although sample preparation and sequencing can be completed in a few days, the genetic analysis of the sequenced exome can take up to months. Therefore, it is crucial to predefine potential genetic targets. In this case a 44-year-old man presented to our nephrological institution with a complex medical history. He has progressive hearing loss and amaurosis since shortly after birth. He suffers from dilatative cardiomyopathy with a strong reduced ejection fraction. A cardiac magnetic resonance imaging study showed a right and left ventricular ejection fraction of around 25% already in the year 2014. Furthermore, he has chronic kidney disease G3bA1 with normal sized kidneys without cysts by computed tomography and an unremarkable urinary sediment, as well as Child–Pugh B cirrhosis. On physical examination he presents overweight (body mass index ~35 kg/m$^2$) with gynecomastia. However, his family history is unremarkable. All his siblings are healthy. Given the complex nature of the patient's medical history, whole-exome sequencing was initiated in our outpatient service, without any results as yet. To accelerate the interpretation of the genetic analysis, we used ChatGPT [3] to obtain potential genetic targets based on the patient's medical history. One such target was the Alström Syndrome 1 gene (*ALMS1*) causing Alström syndrome (AS). This information was subsequently provided to the geneticist, who within just two business days confirmed that the patient actually possesses two distinct mutations in *ALMS1*: c.7783C>T and c.11417_11421delAATTA, both heterozygous and pathogenic. The family history regarding AS-associated diseases was unremarkable.

AS is a rare monogenic ciliopathy caused by biallelic mutations in *ALMS1*. It is inherited in an autosomal recessive manner, with approximately 1200 known cases worldwide. As a multiorgan disorder, it affects different organ systems, such as the eyes, ears, heart, liver, kidneys and endocrine system [4]. Furthermore, *ALMS1* is involved in kidney hemodynamics regulating the tubulo-glomerular feedback mechanism [5]. Early diagnosis of AS is crucial as organ damage occurs at an early age [4]. In concordance with the literature, further laboratory tests have been performed to screen for AS-related complications. The laboratory results revealed a hypergonadotropic hypogonadism with elevated luteinizing hormone (20.9 mIU/mL), follicle-stimulating hormone (22.2 mIU/mL) and low bioavailable testosterone (0.36 ng/mL). Despite elevated levels of C-peptide (9.7 ng/mL), the patient had a normal insulin concentration (10.2 µIU/mL) and a normal HbA1C <6%, thus excluding diabetes mellitus type 2. The hypothalamic–pituitary–adrenal axis showed a normal fasting adrenocorticotropic hormone (38 pg/mL) with slightly elevated fasting cortisol levels (20.4 µg/dL). This patient was diagnosed with AS at a very advanced stage with a poor prognosis. Unfortunately, there is no specific treatment available for AS.

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This case shows that the combination of text-based artificial intelligence tools such as ChatGPT in combination with NGS can accelerate the diagnosis of rare diseases. After providing the geneticist with the information generated from ChatGPT [3], the suspected diagnosis of AS was confirmed within just two business days. For patients with a complex medical background, without a known etiology, the use of ChatGPT together with NGS could be a legitimate and fast approach to the diagnostic process.

## CONFLICT OF INTEREST STATEMENT

None declared.

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