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Ending diagnostic odyssey using clinical whole-exome sequencing (CWES)

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Abstract

Objectives: Most rare diseases are genetic diseases. Due to the diversity of rare diseases and the high likelihood of patients with rare diseases to be undiagnosed or misdiagnosed, it is not unusual that these patients undergo a long diagnostic odyssey before they receive a definitive diagnosis. This situation presents a clear need to set up a dedicated clinical service to end the diagnostic odyssey of patients with rare diseases.

Methods: Therefore, in 2014, we started an Undiagnosed Diseases Program in Hong Kong with the aim of ending the diagnostic odyssey of patients and families with rare diseases by clinical whole-exome sequencing (CWES), who have not received a definitive diagnosis after extensive investigation.

Results: In this program, we have shown that genetic diseases diagnosed by CWES were different from that using traditional approaches indicating that CWES is an essential tool to diagnose rare diseases and ending diagnostic odysseys. In addition, we identified several novel genes responsible for monogenic diseases. These include the *TOP2B* gene for autism spectrum disorder, the *DTYMK* gene for severe cerebral atrophy, the *KIF13A* gene for a new mosaic ectodermal syndrome associated with hypomelanosis of Ito, and the *CDC25B* gene for a new syndrome of cardiomyopathy and endocrinopathy.

Conclusions: With the incorporation of CWES in an Undiagnosed Diseases Program, we have ended diagnostic odysseys of patients with rare diseases in Hong Kong in the past 7 years. In this program, we have shown that CWES is an essential tool to end diagnostic odysseys. With the declining cost of next-generation sequencers and reagents, CWES set-ups are now affordable for clinical laboratories. Indeed, owing to the increasing availability of CWES and treatment modalities for rare diseases, precedence can be given to both common and rare medical conditions.

Introduction

According to the World Health Organization, a rare disease is one that affects a small percentage of the population (i.e., 0.65–1 affected person out of 1,000 individuals). According to the Rare List (<http://globalgenes.org/rarelist/>), 300 million people worldwide have approximately 7,000 rare diseases. Patients with rare diseases typically go through a long diagnostic odyssey due to the challenges that accompany the diagnosis of rare diseases. Over the past 30 years, most of the patients with rare diseases referred to us for genetic testing were either undiagnosed or misdiagnosed. For example, we encountered a patient with Wilson disease, which is a treatable liver disease, who was undiagnosed for 18 years [1]. Another patient received a definitive diagnosis of citrin deficiency as the cause of neonatal jaundice till the age of 14 [2]. On a positive note, we ended the diagnostic odyssey of a family with three adults who have dysferlinopathy that was misdiagnosed as polymyositis and connective tissue diseases for more than 10 years [3]. Further, we identified a *POLG*-related mutation in a patient with mitochondrial recessive ataxia syndrome (includes SANDO and SCAE) misdiagnosed as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [4]. The patient first presented at 8 years of age, and she finally received the correct diagnosis at 18 years of age. In a case such as this, a correct diagnosis can facilitate the provision of appropriate genetic counseling to the family (in this case, inheritance is autosomal recessive, not the maternal inheritance observed in MELAS). The correct diagnosis was beneficial for the patient and her family because they were advised to avoid valproic acid, which is a common anti-epileptic drug that can cause liver toxicity in *POLG*-carriers.

To end the diagnostic odyssey of patients with rare diseases, it is necessary to set up an Undiagnosed Disease Program. The program can provide important insights into the pathogenesis of rare diseases based on the novel gene–disease association. Guided management can then be provided to the patients, and the accuracy of prognosis

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prediction can be enhanced. In the same vein, genetic counseling can be more specific, recurrent risk calculation can be more accurate, and direct screening of complications for early detection and treatment can be initiated. With the advent of next generation sequencing (NGS) technology, many patients with undiagnosed diseases can now enjoy the benefits of a diagnostic tool such as clinical whole-exome sequencing (CWES). Since DNA extraction and generation of NGS libraries can be automated by liquid handlers, a NGS facility for molecular diagnosis can be managed by a single operator. Since de-multiplexing and alignment of NGS reads are performed during sequence runs and processing of data files for variant detection are automated by the sequencers, lack of expertise in bioinformatic analysis is no longer a barrier for the implementation of CWES in clinical laboratories. Taken together, advancements in NGS and bioinformatics technologies enabled the setting up Undiagnosed Disease Programs in clinical laboratories.

In 2014, we started the Undiagnosed Diseases Program in Hong Kong with the aim of ending the diagnostic odysseys of patients and families with rare diseases who do not have a definitive diagnosis after extensive investigation. In this program, we have shown that CWES is an essential tool to end diagnostic odysseys by the minimal overlaps of monogenic diseases diagnosed by CWES and non-CWES/traditional approaches in the past 30 years in the author's laboratory.

Materials and methods

Patients were referred by clinicians specialized in cardiology, endocrinology, genetics, hepatology, metabolic medicine, nephrology, neurology, obstetrics, pathology, and pediatrics. Blood samples were collected from the patient and her family members after informed consent. Genomic DNA was extracted from whole blood samples by the QIAamp blood kit (Qiagen, Hilden, Germany) according to the manufacturer's instruction. Clinical whole-exome sequencing (CWES) was performed using SureSelectXT Human All Exon V4 target kits (Agilent Technologies, Santa Clara, USA) and Nextera kits (Illumina, San Diego, USA) according to the manufacturers' protocols. Sequencing was performed using an Illumina sequencer with 100-bp paired-end module (Illumina). Image analysis and base-calling were performed using the standard Illumina data analysis pipeline. CWES data filtering was performed using VariantStudio (version 2.2.1, Illumina). The in silico prediction of the damaging effects of each single-nucleotide variant were assessed using PolyPhen and SIFT. Variants were filtered based on population frequency, inheritance patterns, and in silico predictions. Resources such as the Human Gene Mutation Database, 1,000 Genomes database, Exome Aggregation Consortium, OMIM, PubMed, and ClinVar were used to evaluate the sequence variants of interest. Interpretation of variants was in accordance with the 2015 American College of Medical Genetics and Genomics

standards and guidelines for the interpretation of sequence variants [5]. The pathogenic variants were described according to the Human Genome Variation Society guidelines on nomenclature for the description of sequence variants (<http://www.hgvs.org/mutnomen>).

Results and discussion

Through the Undiagnosed Disease Program, we were able to identify 42 monogenic diseases diagnosed by CWES and several of them are potentially treatable conditions [6–12] (Table 1). For instance, we identified a genetic defect in the thiamine pyrophosphokinase gene (*TPK1*) using CWES, thereby ending the 40-year diagnostic odyssey of a patient who presented with Leigh-like symptoms [6]. The *TPK1* gene is responsible for encoding thiamine pyrophosphokinase, an important enzyme in thiamine metabolism, and a genetic defect in the *TPK1* gene can lead to episodic encephalopathy. Thus, early dietary intervention/supplementation may reverse or slow down the disease progression. In contrast a total of 106 monogenic diseases were diagnosed by traditional/non-CWES methods in the past 30 years in the author's laboratory [6, 13–116] (Table 1). Through a Venn diagram analysis, we showed that the spectrum of monogenic diseases diagnosed by CWES overlapped minimally with that of diseases diagnosed using non-CWES/traditional laboratory methods (Figure 1). Hence, it is more difficult to diagnose these diseases using clinical and traditional laboratory methods that do not involve CWES.

We also identified several novel genes for monogenic diseases using CWES. The genes include the *TOP2B* gene for autism spectrum disorder [7], the *DTYMK* gene for severe cerebral atrophy [8], the *KIF13A* gene for a new ectodermal syndrome [9], and the *CDC25B* gene for a new syndrome of cardiomyopathy and endocrinopathy [10]. In the case of the *TOP2B* gene, the proband presented with global developmental delay and intellectual disability associated with a *de novo* *TOP2B* mutation. CWES of the proband revealed that she was heterozygous for NM_001068.2:c.172C>T; NP_001059.2:p.His58Tyr of the *TOP2B* gene. The mutation in the patient is a *de novo* mutation. *TOP2B* encodes for the enzyme topoisomerase II isoenzyme beta, which is abundant in the developing brain and in the adult brain. Three years after the publication of this case, an identical *de novo* variant was identified in a Japanese patient with a similar phenotype [117]. In the case of the *CDC25B* gene, the patient was an 11-year-old Chinese girl born to consanguineous asymptomatic parents with a history of one fetal death and one infant death, both of unknown causes. The proband suffered intrauterine

Table 1: Gene panels of diseases diagnosed by CWES and non-CWES/traditional methods. Only *SUOX* and *ABCD1* are shared between the two panels.

(A) A gene panel of 42 diseases diagnosed by CWES	(B) A gene panel of 106 diseases diagnosed by non-CWES/traditional methods
<p><i>ABCD1</i>, adrenoleukodystrophy; <i>AK9</i>, new syndrome; <i>ATP8B1</i>, cholestasis, progressive familial intrahepatic 1; <i>BRAF</i>, cardiofaciocutaneous syndrome; <i>C3</i>, C3 deficiency; <i>CDG25B</i>, new syndrome; <i>COL12A1</i>, Bethlem myopathy 2; <i>COL4A5</i>, Alport syndrome; <i>COQ4</i>, coenzyme Q10 deficiency, primary, 7; <i>COX20</i>, mitochondrial complex IV deficiency, nuclear type 11; <i>CYP7B1</i>, spastic paraplegia 5A, autosomal recessive; <i>DDX3X</i>, Intellectual developmental disorder, X-linked, syndrome, Snijders Blok type; <i>DYMK</i>, new syndrome; <i>EBF3</i>, hypotonia, ataxia, and delayed development syndrome; <i>FBN1</i>, Marfan syndrome; <i>FDXR</i>, auditory neuropathy and optic atrophy; <i>FGFR3</i>, hypochondroplasia; <i>GNAO1</i>, developmental and epileptic encephalopathy 17; <i>GRIN2B</i>, developmental and epileptic encephalopathy 27; <i>GTPBP3</i>, combined oxidative phosphorylation deficiency; <i>IFIH1</i>, Aicardi–Goutières syndrome 7; <i>KDM6A</i>, Kabuki syndrome 2; <i>KIF1A</i>, NESCAV syndrome; <i>KIF13A</i>, new syndrome; <i>KRT17</i>, cerebral cavernous malformations; <i>LCAM1</i>, hydrocephalus due to aqueductal stenosis; <i>LMBRD2</i>, new syndrome; <i>NR2F1</i>, Bosch–Boonstra–Schaaf optic atrophy syndrome; <i>PEX6</i>, peroxisome biogenesis disorder 4A (Zellweger); <i>PIGO</i>, hyperphosphatasia with mental retardation syndrome 2; <i>PURA</i>, neurodevelopmental disorder with neonatal respiratory insufficiency, hypotonia, and feeding difficulties; <i>RAPSN</i>, congenital myasthenic syndrome; <i>RYR1</i>, minicore myopathy with external ophthalmoplegia; <i>SATB2</i>, Glass syndrome; <i>SERPINF1</i>, osteogenesis imperfecta, type VI; <i>SLC16A2</i>, Allan–Herndon–Dudley syndrome; <i>SPTAN1</i>, developmental and epileptic encephalopathy 5; <i>SUOX</i>, isolated sulfite oxidase deficiency; <i>TBC1D24</i>, developmental and epileptic encephalopathy 16; <i>TOP2B</i>, new syndrome; <i>TPK1</i>, thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type); <i>WT1</i>, Frasier syndrome.</p>	<p><i>ABCB11</i>, progressive familial intrahepatic cholestasis-2; <i>ABCC8</i>, hyperinsulinemic hypoglycemia, familial, 1; <i>ABCD1</i>, adrenoleukodystrophy; <i>ABCG5</i>, sitosterolemia; <i>ACADVL</i>, very long-chain acyl-coenzyme A dehydrogenase deficiency; <i>ACTA1</i>, nemaline myopathy 3; <i>AGL</i>, glycogen storage disease type III; <i>AGXT</i>, primary hyperoxaluria 1; <i>ALB</i>, familial dysalbuminemic hyperthyroxinemia; <i>ARG1</i>, arginase deficiency; <i>ALPL</i>, hypophosphatasia; <i>AR</i>, Kennedy syndrome; <i>ARSB</i>, Maroteaux–Lamy syndrome; <i>ASL</i>, argininosuccinate lyase deficiency; <i>ATM</i>, ataxia telangiectasia; <i>ATP2A2</i>, Darier disease; <i>ATP2C1</i>, Hailey–Hailey disease; <i>ATP7B</i>, Wilson disease; <i>AVPR2</i>, X-linked nephrogenic diabetes insipidus; <i>BCHE</i>, butyrylcholinesterase deficiency; <i>CASR</i>, familial hypocalciuric hypercalcemia; <i>CDG73</i>, familial hyperparathyroidism; <i>CHAT</i>, myasthenic syndrome, congenital, 6, presynaptic; <i>CLCN7</i>, malignant infantile osteopetrosis; <i>COL2A1</i>, spondyloepiphyseal dysplasia congenita; <i>COLQ</i>, myasthenic syndrome, congenital, 5; <i>CPT2</i>, carnitine palmitoyltransferase II deficiency; <i>CYP17A1</i>, steroid 17 alpha-hydroxylase deficiency; <i>CYP21A2</i>, adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency; <i>CYP27A1</i>, cerebrotendinous xanthomatosis; <i>DMPK</i>, myotonia congenita; <i>DPYD</i>, dihydropyrimidine dehydrogenase deficiency; <i>DYT1</i>, primary torsion dystonia; <i>FAH</i>, tyrosinemia type II; <i>HLCS</i>, holocarboxylase synthetase deficiency; <i>HMBS</i>, acute intermittent porphyria; <i>HPRT1</i>, Kelley–Seegmiller syndrome; <i>HTT</i>, Huntington disease; <i>IDS</i>, Hunter syndrome; <i>IDUA</i>, Hurler syndrome; <i>IVD</i>, isovaleric acidemia; <i>KCNE2</i>, Long QT syndrome 6; <i>KCNJ1</i>, antenatal Bartter syndrome type II; <i>KCNQ1</i>, long QT syndrome type I; <i>KRT17</i>, steatocystoma multiplex; <i>LPL</i>, lipoprotein lipase deficiency; <i>MECP2</i>, Rett syndrome; <i>MMACHC</i>, methylmalonyl CoA mutase deficiency, methylmalonic aciduria and homocystinuria (b1c type); <i>MOCS1</i>, molybdenum cofactor deficiency A; <i>mtDNA</i>, Kearns–Sayre syndrome/Leber hereditary optic neuropathy/Leigh syndrome/ mitochondrial encephalomyopathy with lactic acidosis and stroke syndrome/Pearson syndrome; <i>MUT</i>, methylmalonic aciduria, mut(0) type; <i>MVK</i>, mevalonic aciduria; <i>NAGLU</i>, mucopolysaccharidosis type IIIB; <i>NPHS1</i>, congenital nephrotic syndrome type 1; <i>NR0B1</i>, congenital adrenal hypoplasia; <i>OTC</i>, ornithine transcarbamylase deficiency; <i>PANK2</i>, pantothenate kinase 2 deficiency; <i>PARK2</i>, juvenile parkinsonism; <i>PDCN</i>, congenital nephrotic syndrome type 2; <i>PHKA2</i>, glycogen storage disease type IX; <i>POLG</i>, mitochondrial recessive ataxia syndrome (includes SANDO and SCAE); <i>POMT1</i>, muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B; <i>PPOX</i>, variegate porphyria; <i>PROS1</i>, protein S deficiency; <i>PRRT2</i>, episodic kinesigenic dyskinesia 1; <i>PTCH1</i>, basal cell nevus syndrome; <i>PTPN11</i>, LEOPARD syndrome; <i>PYS</i>, 6-pyruvoyl-tetrahydropterin synthase deficiency; <i>RYR2</i>, catecholaminergic polymorphic ventricular tachycardia; <i>SCN1A</i>, Dravet syndrome; <i>SCN4A</i>, paramyotonia congenita; <i>SDHD</i>, succinate dehydrogenase deficiency; <i>SLC12A1</i>, antenatal Bartter syndrome type I; <i>SLC12A3</i>, Gitelman syndrome; <i>SLC25A13</i>, citrin deficiency; <i>SLC25A15</i>, hyperornithinemia–hyperammonemia–homocitrullinuria syndrome; <i>SLC25A20</i>, carnitine–acylcarnitine translocase deficiency; <i>SLC26A4</i>, Pendred syndrome; <i>SLC37A4</i>, glycogen storage disease type Ib; <i>SLC3A1</i>, cystinuria; <i>SLC4A1</i>, distal renal tubular acidosis; <i>SLC7A9</i>, cystinuria; <i>SMN1</i>, spinal muscular atrophy; <i>SRD5A2</i>, 5-alpha reductase deficiency; <i>SUOX</i>, isolated sulfite oxidase deficiency; <i>TAZ</i>, Barth syndrome; <i>TH</i>, tyrosine hydroxylase deficiency; <i>THRB</i>, resistance to thyroid hormone syndrome; <i>TPP1</i>, classical late-infantile neuronal ceroid lipofuscinosis; <i>TTR</i>, familial amyloidotic polyneuropathy type 1; <i>URAT1</i>, renal hypouricemia; <i>VHL</i>, von Hippel–Lindau syndrome; <i>XPC</i>, xeroderma pigmentosum type C.</p>

Figure 1: A Venn diagram of gene panels of diseases diagnosed by CWES and non-CWES/traditional methods in the author's laboratory in the past 30 years.

CWES group: a gene panel of 42 diseases diagnosed by CWES; Traditional group: A gene panel of 106 diseases diagnosed by non-CWES/traditional methods. The gene lists are shown in Table 1.

growth retardation, delayed development, bilateral cataract (at 5 years of age), primary hypothyroidism, growth hormone deficiency, and cardiomyopathy (at 9 years of age). CWES of the proband was performed, and we identified a novel homozygous nonsense variant of the *CDC25B* gene known as NM_021873:c.313G>T (p.Glu105*). The c.313G>T in the proband was expected to produce a truncated protein that is terminated at codon 105 with a loss of phosphorylation sites. We posit that a loss-of-function *CDC25B* gene will result in a new syndrome characterized by cataract, dilated cardiomyopathy, and multiple endocrinopathies. In the case of the *DTYMK* gene, the patients were two brothers aged one and 6 years who presented with microcephaly, marked cerebral atrophy with bilateral subdural hemorrhagic effusion, hypotonia, severe intellectual disability, and lactic acidosis. Two mutations in the *DTYMK* gene were identified in the brothers. The first mutation is the frameshift mutation NM_012145.3:c.287_320del;p.Asp96-Valfs*8 and the second one is the missense mutation NM_012145.3:c.295G>A;p.Ala99Thr. In the case of the *KIF13A* gene, the patient was a three-year-old girl who presented with developmental delay and hypomelanosis of Ito. An exome-and-genome approach revealed a heterozygous *de novo* frameshift variant in the *KIF13A* gene (i.e., NM_022113.6:c.2357dupA). The low mutant allelic ratio suggested that the mutation occurred postzygotically, leading to embryonic mosaicism. We suggest *KIF13A* may be the culprit gene in chr 6p22.3–p23 microdeletion syndrome because skin hypopigmentation has been reported in patients with the syndrome [118].

Conclusions

With the incorporation of CWES in an Undiagnosed Diseases Program, we have ended diagnostic odysseys of patients with rare diseases in Hong Kong in the past 7 years. With the technological advancement of NGS, CWES can now be completed in a clinical laboratory in 2 days. In addition, with the declining cost of next-generation sequencers and reagents, CWES set-ups are now affordable for clinical laboratories and precedence can be given to both common and rare medical conditions.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' institutional review board (UW21-150).

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