Whole-Genome Sequencing Informs Treatment: Personalized Medicine Takes Another Step Forward

Karen E. Morrison1,2*

Personalized medicine has long been a key therapeutic goal, harnessing the best treatments for an individual to maximize benefit while minimizing risk. Approaches to achieving such personalized therapy have included analyses of specific genes with therapeutic implications in specific disorders, such as the analysis of genetic testing of polymorphisms in CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) in individuals being prescribed clopidogrel, as discussed in a recent Perspective article in this journal (1). In my own clinical area of neurology, a recent report stated that the effect of the drug entacapone, which inhibits catechol-O-methyltransferase, in prolonging the effectiveness of L-dopa in Parkinson disease is enhanced in patients with specific polymorphisms in this enzyme (2). The time when we routinely screen for certain genetic variants in specific genes before starting therapies will surely not be far off. In the next phase, with DNA-sequencing costs decreasing further and advances in computing methods for sequence analysis pushing ahead, whole-genome sequencing (WGS)4 is poised to take personalized medicine a stage further. Within a year or two, physicians may be presented with patients armed with their full genetic profiles, seeking advice about the best treatments for their specific circumstances.

In the last few months, 2 specific reports have caught my eye, both of which illustrate how the use of WGS has already directly produced beneficial change in patients’ clinical management. The first report is from a study by Bainbridge et al. published in Science Translational Medicine (3), in which WGS was used to first identify the genetic basis for a disorder in a family, in this case L-dopa-responsive dystonia (DRD), and then to provide a rationale for a specific treatment intervention. Dystonia is the term used to describe a clinical disorder of sustained muscle contractions with repetitive twisting movements and abnormal postures of the trunk, neck, face, and legs. DRD is one subtype of dystonia characterized by onset in childhood or adolescence and by marked fluctuations in severity, tending to be worse as the day progresses and relieved by sleep. Another feature of this variant is its usually dramatic response to treatment with low doses of L-dopa, although not all symptoms may be completely relieved (4). DRD can be inherited as either an autosomal dominant or a recessive trait and is most often caused by autosomal dominant point mutations or, more rarely, deletions in the GCH1 (GTP cyclohydrolase 1) gene, which encodes the GCH1 enzyme. Less frequently, the disorder is associated with autosomal recessive mutations in the TH (tyrosine hydroxylase) or SPR (sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase)) gene. Usually, the clinical presentation is of a DRD-plus syndrome, with more complex features such as mental retardation and parkinsonism (4).

The GCH1 enzyme is involved in the rate-limiting step of tetrahydrobiopterin (BH4) synthesis (Fig. 1) by catalyzing the formation of dihydrosperopterin triphosphate from GTP. SPR catalyzes the formation of BH4 from 6-pyruvoyl-tetrahydropterin. BH4 is used as a cofactor for tyrosine and tryptophan hydroxylases, which are involved in the biosynthetic pathways for dopamine and noradrenaline. TH catalyzes the conversion of tyrosine to L-dopa, a precursor of both dopamine and noradrenaline.

Bainbridge et al. (3) detail their findings of compound heterozygous mutations in the SPR gene in a pair of 14-year-old fraternal DRD twins by using WGS. The phenotype of the twins was that of complex DRD, and in that the female twin showed features in addition to DRD, such as rigidity, tremor, and seizures, whereas her more mildly affected brother also showed features of cerebral palsy. Pedigree analysis suggested that the disease was segregating as an autosomal recessive disorder, and both twins had previously undergone screening of the GCH1 and TH genes, both of which were normal. At the time of the study, the authors did not have a clinical sequencing service for SPR, so they proceeded to WGS of the twins. Their analysis of the shared sequence variants of the twins and comparison

1 University of Birmingham, Birmingham, UK; 2 Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

* Address correspondence to the author at: School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Fax +44-121-414-4509; e-mail k.morrison@bham.ac.uk.

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1 Human genes: CYP2C19, cytochrome P450, family 2, subfamily C, polypeptide 19; GCH1, GTP cyclohydrolase 1; TH, tyrosine hydroxylase; SPR, sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase); PML, promyelocytic leukemia; RARA, retinoic acid receptor, alpha.

2 Nonstandard abbreviations: WGS, whole-genome sequencing; DRD, L-dopa-responsive dystonia; BH4, tetrahydrobiopterin.
with the reference genome eventually narrowed the search to only 3 genes that contained 2 or more predicted amino acid–altering heterozygous mutations. One of these genes was SPR. The 2 identified SPR mutations had previously been reported in families with DRD. The 2 mutations were subsequently confirmed as present in a compound-heterozygous state in each twin, and each mutation was confirmed to be present in the heterozygous state in each of the parents.

So far, so good. The study of the identification of these mutations illustrates the power of WGS in identifying autosomal recessive mutations, even if the mutations, as in this case, could have been identified if SPR screening had been undertaken initially as part of a candidate gene–screening approach. As the authors stated, however, candidate gene screening has drawbacks that WGS does not (4). These drawbacks including failing to pick the right genes to analyze in the first place, not analyzing all biologically important areas of the gene (such as untranslated regions and promoters), and not eliminating other genes from consideration. Additionally, candidate gene screening can be as time-consuming and expensive as WGS, or more so, depending on the number of candidates selected for analysis.

What makes the study by Bainbridge et al. particularly noteworthy, however, is how the identification of the genetic mutations was then used to inform a treatment change. Before the genetic analysis, at age 14 years, both twins were being treated solely with L-dopa. Although both were doing well academically, both continued to have mild dystonia and other neurologic symptoms. SPR is required for the biosynthesis of BH4, which is subsequently used in the pathways for the synthesis of dopamine, serotonin, and tyrosine (Fig. 1). The results of the genetic testing prompted a change in their treatment to include 5-hydroxytryptophan, which was previously shown to be effective in improving symptoms in DRD due to SPR mutations. Within a few weeks of adding the 5-hydroxytryptophan treatment, symptoms in both twins had improved and these improvements were sustained to at least 4 months, when the report was written. One could perhaps quibble that it is not clear whether the assessments after the change in treatment were undertaken by a blinded assessor and that no objective measures of improvement are given. Nevertheless, the treatment change, a consequence of the WGS results, seems to have yielded clear clinical benefit.

Another recent example of how WGS has altered patient management is in the area of oncology, as provided in the report by Welch et al. (5). These authors report the use of WGS in a 39-year-old woman who presented with acute myeloid leukemia. Although the results of her initial bone marrow studies suggested that she had acute promyelocytic leukemia, a subtype of acute myeloid leukemia with a good prognosis, a subsequent cytogenetic analysis revealed a complex case of a complex genomic rearrangement involving multiple breakpoints and additional abnormalities, which was not evident from the initial cytogenetic analysis. WGS enabled the identification of these additional abnormalities, leading to a revised treatment plan that included targeted therapies specifically designed to address the specific genetic abnormalities identified by WGS. This example highlights the potential of WGS in personalizing treatment strategies for patients with cancer, which can lead to improved outcomes and reduced side effects.
pattern associated with a poor prognosis, and she was referred for consideration for bone marrow transplantation. Subsequently, WGS of DNA isolated from her initial leukemic bone marrow aspirate and from her skin biopsy obtained when the patient was in remission led to the identification of a novel insertion-translocation on chromosome 17 that produced a pathogenic fusion of the \textit{PML} (promyelocytic leukemia) and \textit{RARA} (retinoic acid receptor, alpha) genes (i.e., \textit{PML-RARA}), an abnormality that was not visible from the cytogenetic studies. Identification of this gene fusion meant that her treatment plan was radically altered from one of bone marrow transplantation to a chemotherapeutic regimen. Importantly, this report indicated that the timeline for analysis was very fast—only 25 days to generate and analyze the WGS and then 27 days for validation of the findings. The authors propose that with increasingly deep WGS coverage, the need for validation of findings may be reduced and that WGS results may be available within 4 weeks of sample collection. Such a rapid time frame could mean that WGS could fit well into the clinical management plans of several cancers, even those in which urgent chemotherapy is required.

Of course, WGS does not come without challenges. A key issue is the managing of informed consent for such studies. Such consent requires a competent patient to be provided with correct information about the likely outcome of such studies, the weighing of risks and benefits, and the discussion that much of the sequence information generated will have unknown meaning and importance. Important considerations include how much information to transmit back to an individual and who has the necessary skills and time to deliver this information. For the 2 cases described in these reports (3, 5), the issues were relatively straightforward. The data recognized to be of immediate clinical relevance were transmitted back to the clinical teams caring for the patients and thence to the patients and parents. But what of the rest of the data generated? At what point, if ever, should this information be given to the patients? Considering WGS in the context of screening of healthy individuals who have no specific medical question but want general advice and counseling about their overall risks for a huge variety of disorders is an entirely different ball game, and the rules for refereeing still need to be written.

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