DNA needs a doctor: genomics review and commentary

Golder N Wilson*
Kinder Genome Genetics, Dallas TX and Clinical Professor of Pediatrics, Texas Tech Health Sciences Center, Lubbock, USA

Introduction

Had we but world enough, and time,
This coyness, Lady, were no crime.
We would sit down and think which way
To walk and pass our long love’s day
...

The grave’s a fine and private place,
But none, I think, do there embrace.
Now therefore, while the youthful hue
Sits on thy skin like morning dew,
Rather at once our time devour
Than languish in his slow-chapt power [1]
...

DNA is a coy mistress, difficult to interpret, devouring too much time for busy practitioners. Yet technology’s power in the form of genomic testing [2,3] (Table 1) is now so all-encompassing that no caring physician would let their families languish in molecular confusion. Genomics can postpone the grave’s embrace, its pivotal impact on reproduction and pregnancy justifying a feminine metaphor.

While many phases of genomic testing [4] (Table 2) remain in their youthful hue it is particularly necessary that the doctor code walk DNA tests from rare disease to population screen. Genomics can reach every family and define any genetically influenced disease, so it must be embraced by medicine at large and not remain a private place for ward-deprived genetic counselors and lab-contained geneticists. The tables and case examples should remind physicians that 2D DNA becomes coy and complex only when correlated with 4D disease, the essence of general medicine. Physician experience will be just as necessary to place the many results from DNA analysis into patient context as it is to interpret those of a sequential multi-channel analysis with computer-20 (SMA20) panel.

DNA is the common denominator unifying previously separate testing categories like karyotyping for children with birth defects, blood/urine chemistries for suspected metabolic disease, or specific subspecialty tests like those for cystic fibrosis in pulmonology/perinatology, spinal muscular atrophy in neurology, or for the Philadelphia chromosome in oncology [2]. Now general physicians can initiate testing for these various disease categories because all can be diagnosed by the same genome-scanning test: whole exome sequencing (WES) that looks simultaneously for extra/missing chromosome segments (formerly done by karyotyping or microarray analysis) and for “typos” in the DNA nucleotide GATTACA sequence that makes its encoded protein dysfunctional (Table 1). Subspecialists will be involved in the testing for rarer diseases and categories, but family physicians are invaluable for deciding when and which types of testing/subspecialty evaluations are best for families. Even more important is their translation of results into the prevention and monitoring strategies of a medical home.

Six phases of modern genetic testing

The first genetic tests began with a suspect diagnosis, confirmed by demonstrating altered structures of targeted genes or their protein products. Children with likely Down syndrome had extra chromosome 21 DNA by karyotype and then microarray, those with anemia and crises had abnormal hemoglobin S, those with intellectual disability and mousy smell had elevated plasma phenylalanine. Newborn screening included the latter two disorders and prenatal sampling of fetal cells allowed testing for all three disorders once DNA made any tissue suitable for testing.

Array formats and NextGen techniques accelerated DNA sequencing from thousands to millions of nucleotides per day, allowing screening of all 23 chromosome pairs for abnormal dosage and most of the 23,000 genes for abnormal nucleotide sequence (Table 1). Six phases of genetic testing can be outlined (Table 2), all of them potentially involving new approaches to medical testing: Screening that avoids the presumption of diagnosis and pre-symptomatic diagnosis that transcends the presumption of disease.

It is the general physician who strives to know the general world of medicine, and their time, though limited, can make a huge difference for families as shown by the following case examples. Supporting this valuable service are accessible web resources that offer describe clinical symptoms and DNA changes for any genetic disease [5], outline symptom patterns for particular DNA dosage changes/ chromosome disorders [6], give details on genes and their DNA sequence changes [7] for those seeking more detail than laboratory reports provide.

Case 1:A boy with speech delay

A 3-year-old boy had mild motor but significant speech delay along with sensitivity to loud or background noises, early reflux and feeding difficulties with textural sensitivity, poor eye contact and socialization with aggressive behaviors in preschool. Gestational, medical, and family histories were otherwise normal and physical examination showed no facial or physical anomalies with growth at the 50th centile for height and head size, 80th centile for weight.

*Correspondence to: Golder N Wilson, Kinder Genome Genetics, Dallas TX and Clinical Professor of Pediatrics, Texas Tech Health Sciences Center, Lubbock, USA, E-mail: Golder.Wilson@ttuhsc.edu

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Microdeletion 16p11.2 qualifies as a known pathogenic (disease-causing) change, associated with a pattern of developmental delays with autonomic behaviors and obesity [8]. It also suggested parental studies to exclude mild expression and risks for future children, a family study ideally coordinated or explained by the primary physician. Equally important would be counsel that an autism diagnosis must be confirmed by usual assessment scales rather than being inferred from a genomic test [9].

Case 2: Child with thrombocytopenia

A 2-year-old boy had frequent respiratory infections despite normal gestational, birth, and developmental histories. Bruising and nosebleed had occurred with several of these infections and a fourth infection in three months with petechiae over his upper body and trunk led to pediatric evaluation. Values for hemoglobin of 11 g/dL,
white blood cell count of 6500/μL with low neutrophils, and platelet count of 5,000/μL led to the presumptive diagnosis of idiopathic thrombocytopenic purpura (ITP). Improved but not normal platelet counts (~ 80,000/μL) were obtained after immunoglobulin and steroid therapy, but continued episodes led the parents to seek genetic evaluation to define the basis of disease and risks for their next pregnancy.

Although mother’s maternal uncle had similar ITP episodes while young, healthy now in his 40s, I felt their risk was only 3-5% for ITP in future children as would be the case for most common multifactorial disorders (diabetes, schizophrenia, isolated birth defects, etc.) that involve many genetic and environmental factors. The parents proved wiser and asked for genetic testing, WES showing that the WAS gene associated with Wiskott-Aldrich syndrome [10,11] had a DNA letter change at nucleotide 741 that altered its code from polar glutamic acid (glu or E in amino acid code) to non-polar cysteine (cys or C). The mutation was reported as definitely pathogenic because it is an identical mutation [10]
had been observed in a child with Wiscott-Aldrich syndrome; 2) it was present in his asymptomatic mother and likely her brother with ITP as expected for an X-linked condition; and 3) the boy’s symptoms of frequent infections, thrombocytopenia, and neutropenia correlated well with those of Wiscott-Aldrich syndrome.

The primary physician would be important in coordinating specialty care that included new treatment options [standard bone marrow or novel stem-cell transplant/gene therapy-11] and reinforcing the 25% risk for future children along with reproductive options.

Case 3: Woman with joint pain and chronic fatigue

A 28-year-old woman returned to her primary physician after several years of unexplained joint pain and fatigue, discouraged by multiple subspecialty evaluations that found no diagnosis. She began having joint pain as a child, dismissed as “growing pains” by her parents and physicians, and had a long history of constipation and stomach pain that had been attributed to stress. She had frequent sprains, several fractures, knee ligament tears, and lumbar disc herniation that required various surgeries. She had persisted in exercise and activity despite her pain but became extremely fatigued after her first pregnancy. She tried to return to work but found that she had trouble making it through the week, often collapsing Friday evenings and remaining exhausted all weekend to the detriment of her husband and new child. She developed episodes of tachycardia and anxiety that had rarely occurred during childhood, and disturbed sleep contributed to her fatigue. Rheumatology found no evidence of autoimmune disease, gastroenterology normal endoscopy except for mild inflammation, and cardiology no signs of arrhythmia or structural defects.

Her primary had supported her several years of evaluation and recognized that she had an underlying disease, referring her to genetics. I documented hypermobility on examination and suspected a form of Ehlers-Danlos syndrome (EDS), doing whole exome sequencing that documented a mutation in the collagen type V alpha-1 chain (COL5A1) gene, a common cause of EDS [12,13]. Armed with this DNA diagnosis the patient and her primary were able to find new subspecialists who recognized her osteoarthritis due to joint laxity, irritable bowel syndrome (IBS) with constipation/bowel immotility, and postural orthostatic tachycardia syndrome (POTS) causing tachycardia, insomnia, and chronic fatigue [12]. Therapy for these complications from autonomic nervous system imbalance included beta-blockers with fluid-salt and gluten/dairy exclusion dietary strategies that restored the woman’s work and family life [13-20].

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