

Several rare congenital syndromes can soon be diagnosed more rapidly than before. New sequencing technology makes it possible to analyse a selection of, or all, our 22 000 genes simultaneously. We are on the brink of a shift in diagnostic paradigm.

A diagnostic revolution

This issue of the Journal of the Norwegian Medical Association features a discussion of the treatment of congenital webbed fingers, syndactyly (1). As with other structural congenital anomalies, syndactyly may be an isolated phenomenon or part of a congenital syndrome. When something is wrong with their child, parents will ask: Why did this happen? How will it affect our child? What can be done? Can it happen again? An aetiological diagnosis is not an exact answer to these questions, but provides a good basis for addressing the issues.

Thousands of congenital syndromes have been described. When a cause is known, it is often genetic. Suspicion of a congenital syndrome is raised by a combination of factors such as an abnormal growth pattern, unusual physical characteristics, organ malformations, delayed development and cognitive impairment. The family history may reveal relatives with similar problems or parental consanguinity. In some cases, the clinician's deliberations will result in a probable diagnosis such as Williams syndrome, Prader-Willi syndrome or Angelman syndrome, and targeted testing of one or several relevant genes can be ordered. However, even in the best of hands this diagnostic approach – from phenotype to genotype – succeeds in barely half of cases. Now a paradigm shift is taking place: genetic testing will be done first and be followed by clinical review; in this way many more patients will be diagnosed.

Viewed individually, congenital malformations and syndromes are rare, but overall they are frequent. In approximately 8 % of live births a congenital anomaly and/or a genetically conditioned syndrome is detected by the age of 25 (2). Genetic causes of congenital syndromes are divided into two main categories with partial overlap: single gene defects and chromosomal abnormalities. The latter usually involve several genes. More than half of all chromosomal abnormalities are not visible by light microscopy, but may be detected with the help of DNA-based chromosomal analysis. Cumulatively, submicroscopic chromosomal abnormalities of this type are far more frequent than, for example, Down syndrome.

The strategy when a genetic syndrome is suspected has until now been to test one or more selected genes, based on the clinical phenotype. Although this strategy can be very resource intensive, it is nonetheless used because a specific diagnosis may have consequences for prognosis, treatment and family planning. What is new is that genetic testing will be moved towards the front of the diagnostic process. When there is suspicion of a congenital syndrome, genetic testing will often be ordered *before* a specific diagnosis is suggested. More diagnoses will be made, and they will be made much faster than previously. Much of the diagnostic intellectual work will take place *after* instead of *before* the genetic testing. This is a result of new sequencing technology, often called next-generation sequencing, which enables the analysis of a selection of, or all, our 22 000 genes simultaneously.

The introduction of next-generation sequencing has until now been impeded by the cost of laboratory analyses, a shortage of suitable bioinformatic tools and of hospital-based bioinformaticians, insufficient information in databases of normal and pathological genetic variants, long turn-around times and the suboptimal sensitivity of laboratory analyses. These problems are now being resolved thanks to international collaboration and the ongoing improvement in available methods.

One concern relates to the detection of so-called incidental findings, i.e. genetic variants which may have health-related consequences, but which are not relevant to the problem the patient is being investigated for. In a newborn being investigated for a congenital syndrome, for example, a genetic variant could be detected that is associated with a significantly increased likelihood of cancer in adulthood. Such incidental findings will probably occur in a small percentage of those being investigated. The issue is not new: incidental findings are also detected, for example, by cerebral MRI or DNA-based analyses for submicroscopic chromosomal abnormalities. Incidental findings during genetic investigations should be manageable within the context of the doctor-patient relationship. The doctor must discuss the possibility of, and approach to, incidental findings with the patient or her guardians before the investigation is ordered. Work on guidelines which address this issue is in progress (3).

Combining clinical expertise, next-generation sequencing and bioinformatic analysis has proven to be a good diagnostic strategy. An American research group has demonstrated that next-generation sequencing can be used to diagnose ill newborns rapidly and affordably (4). At the National Institutes of Health Undiagnosed Diseases Program this method was crucial to enabling diagnosis of six of 32 patients who had previously been thoroughly investigated with conventional diagnostics (5).

It is realistic to expect to achieve an etiological diagnosis with next-generation sequencing in around one-third of patients with congenital syndromes who have already been investigated in accordance with standard practice. However, next-generation sequencing will not solve all diagnostic puzzles. Genetic variants that are detected must be interpreted in light of clinical findings. For many patients the method will not provide a diagnosis, and in the worst case scenario a misdiagnosis may be made because a benign genetic variant is misinterpreted as pathological. Clinical geneticists will continue to act as a bridge between other specialists, the laboratory and researchers. One of their important tasks will be to tell the laboratory that the map does not fit the terrain, i.e. that the clinical significance of a genetic variant has most likely been incorrectly interpreted. Clinical diagnosis of syndromes will therefore be far from superfluous, in fact it may become even more important, but will be moved to a later stage in the diagnostic process.

What skills must «next generation» clinical geneticists have? In addition to being good clinicians they must be familiar with new sequencing technology, be adept at interpreting genetic and genomic variants, have insight into both the complexity of genetics and biological processes, and be good communicators.

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