

Whole Exome Sequencing

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Our goal is to highlight annually a methodology of significance to the journal's domains, either because it has been used clinically or researchwise for our fields of interest or because it holds promise as a tool in diagnosing, treating, or investigating corresponding diseases.

We hope another strength of this new section is simplicity of language that can be readily grasped by our readers.

THERE IS little doubt that improved understanding of the genetic basis of disease will continue to produce considerable advances in patient care. Among the genetic tools finding greater application is whole exome sequencing.

Exons account for only 1.2% of a patient's total DNA but contain 85% of all disease-causing mutations found to date.^{1,2} Thus, sequencing all exons (the exome), rather than a person's entire genome, is more rapid (~2–4 weeks) and cost-effective (~\$1000 per person), with both parameters decreasing.

How are exomes sequenced?

A patient's DNA is sheared into small fragments (~200 base pairs) and hybridized (bound) to prefabricated DNA probes. The hybridized exons are captured (again bound) by antibody-marked beads. These exons are then purified and amplified using polymerase chain reaction and finally sequenced using high-throughput sequencing machines.

How are mutations discovered from exome sequences?

Exomes sequenced from the patient are mapped against a reference human genome, and deviations from the reference are identified (~10,000 per person). After excluding common variants known from control libraries, the remaining rare

distinct variations become candidates for potentially disease-causing mutations.

In which disorders of dermatologic significance has exome sequencing uncovered the genetic defect?

Familial cases of psoriasis were shown to have multiple activating mutations of CARD14 that cause enhanced activation of NF- κ B.^{3,4}

A case of oculocutaneous albinism and neutropenia was found to carry 2 gene mutations, *SLCA5A2* and *G6PC3*.⁵

Mutations of *DHOHD* cause Miller syndrome, a rare disorder comprised of eyelid coloboma, severe micrognathia, cleft lip/palate, supernumerary nipples, and hypoplasia or aplasia of the limbs.⁶

What are the strengths and weaknesses of and alternative strategies to exome sequencing?

Exome sequencing is excellent for identifying causative genes of highly penetrant mendelian diseases and for identifying single-nucleotide variations.

However, it may miss variations in nontranscribed regions of the genome (ie, promoters and regulatory elements) and variations that lead to absent transcripts. It may not recognize deletions, duplications, or translocations of genomic DNA causing disease. Finally, it is unable to evaluate variations regulated epigenetically (eg, DNA methylation and histone modification).

Alternatives and complimentary approaches to identifying disease-causing genes include whole genomic sequencing, linkage analysis, searching for copy number variation, and epigenetic testing.

Ethical considerations raise the following questions

Should patients have access to their sequencing information? How about insurance providers? Aside from the gene(s) of interest, what should be done with other unique sequence variations in a given individual?

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