Genetic tests for common diseases: new insights, old concerns

The clinical utility of newly identified genetic variants associated with common diseases needs evaluation say, **David Melzer and colleagues**

Genome-wide studies have recently identified many new variants associated with common diseases. Findings point mainly to sets of variants with modest effects, with many more markers still to be discovered. Some variants are shedding new light on disease mechanisms and on previously unsuspected parts of the genome. Much more work is needed, however, to define the clinical relevance and value to patients of testing for these new genetic markers. It is worrying that in the absence of this knowledge, commercial genetic testing services are being marketed directly to the public. In this paper we describe key findings from the new genome-wide association studies; draw attention to the currently weak regulatory systems, particularly in Europe; and argue the case for improved evaluation, greater transparency, and better regulation, so that the new genetic tests can be used in a safe and informed way.

Environmental factors are major contributors to the development of most common diseases. However, conditions including myocardial infarction, type 2 diabetes, asthma, and even the ageing process itself are influenced by inherited variations in DNA sequence.[1] The most common DNA variant is the substitution of a single base pair: when these occur at a population prevalence of 1% or more; they are termed single nucleotide polymorphisms or SNPs (pronounced "snips"). More complex variants exist, including deletions, insertions, and copy number variations, but most of the recent work on the genetics of common diseases has focused on SNPs.

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Accepted: 23 January 2008

In tandem with the sequencing of the human genome, extraordinary advances have occurred in the technology for determining the status of SNPs. The original wet laboratory techniques gave way to robotic systems and then to miniaturisation. The latest format has test probes arrayed on the surface of a chip, able to analyse more than a million SNPs simultaneously, capturing over 95% of common variation.[2]

Flood of discoveries

During the 20th century many inherited mutations of single genes were discovered, often by studying families in which several relatives were affected. In such conditions, the genotype can be synonymous with the diagnosis. But many common diseases are polygenic, with many variant genes playing a part. The family (linkage) studies used to identify the responsible variants lacked power to detect modest effects. Association studies of unrelated cases and controls have become popular, but early association studies seriously underestimated sample sizes and many findings did not replicate. A large study of 85 SNPs that had been claimed to be associated with myocardial infarction, for example, found little evidence for any.[3] Genetic association studies looked discredited.

In the past 18 months, with a flurry of robustly designed "genome-wide" association studies, the field has been transformed. Current studies have typically determined more than 500 000 SNPs across the genome in thousands of participants. Promising associations are thoroughly replicated, typically with tens of thousands of cases and controls, allowing genome-wide statistical significance (typically $P<0.0000001$) to be achieved, accounting for the large numbers of SNPs examined.

Many new variants associated with polygenic conditions as well as traits such as body mass index, height, and even skin pigmentation (table 1) have now been identified, mainly by genome-wide studies. In a few conditions, markers of moderate risk have been identified. The incidence of age related macular degeneration in people of European origin with two risk alleles (homozygous) for a complement factor H SNP is six times that in those with no risky allele.[4] Similarly, the 4.1% of Europeans who have a R501X or 2282del4 mutation in the filaggrin gene (which produces a keratin linking protein in skin) have four times the risk of atopic eczema and are at higher risk of severe asthma.[5]

In most cases, however, risks have been smaller. People homozygous for the risk allele with the largest effect associated with myocardial infarction[6] (near p15/p16 on chromosome 9) have a 64% increase in risk, and those homozygous for a TCF7L2 SNP have up to

Table 1 | Selected recent findings, mainly from genome-wide association studies

Disease	Chromosomal region or Gene implicated
Age related macular degeneration[w1]	1q32 (CFH) and 10q26 (LOC387715/ARMS2)
Atrial fibrillation[w2]	4q25 (close to PITX2)
Asthma[w3]	ORMDL3
Atopic eczema and asthma[w4 w5]	Filaggrin
Breast cancer[w6]	FGFR2, TNRC9, MAP3K1, LSP1, H19
Colorectal cancer[w7 w8]	8q24.21
Coronary heart disease/ myocardial infarction[w9 w10]	9p21 (close to p15/p16 CDKN2A/CDKN2B)
Crohn's disease[w11]	ATG16L1, PHOX2B, NCF4, and a predicted gene on 16q24.1 (FAM92B), CARD15, IL23R
Type 1 diabetes[w12]	12q24, 12q13, 16q13, and 18q11, CTLA4, major histocompatibility complex locus
Type 2 diabetes[w13]	TCF7L2, CDAL1, CDKN2B, IGF2BP2, HHEX/IDE, SLC30A8, FTO, etc
Gall stone disease[w2]	ABCG8
Multiple sclerosis[w14]	IL2r, IL7-alpha, and ILA-DRA
Prostate cancer[w15]	8q24 and 17q
Restless leg syndrome[w16 w17]	MEIS1, BTBD9, locus between MAP2K5 and LBXCOR1
Rheumatoid arthritis[w18]	6q23, major histocompatibility complex locus
Systemic lupus erythematosus[w19]	IRF5
Traits	
Body mass index (obesity)[w20]	FTO
Height[w21]	HMGA2
Eye, hair, and skin pigmentation (in northern Europeans)[w22]	SLC24A4, KITLG, TYR, 6p25.3, OCA2, MC1R

References w1-w22 are on bmj.com

double the risk of type 2 diabetes.[7] More than 10 other markers for type 2 diabetes have been discovered, most increasing risks by less than 20%.

These findings are remarkable in many ways. Although some known gene variants were confirmed, several unexpected loci emerged, sometimes in poorly understood regions and genes. This opens entirely new scientific directions, which may ultimately lead to new interventions.

In some cases the SNP findings provide insight on the cause of disease—for example, most of the SNPs for type 2 diabetes are associated with impaired beta cell function,[8] and the filaggrin mutations associated with allergies compromise the skin barrier.[5] In some cases the genes that have been identified point to surprising overlaps in aetiology. Separate SNPs for myocardial infarction and type 2 diabetes were identified near the p15/p16 genes (also called CDKN2a/2b or INK4a/4b). These genes regulate cancer suppressor pathways, harbour mutations for familial malignant melanoma,[9] and are implicated in the biology of ageing.[10 11]

Clinical potential

Although major scientific progress has been made, clinical applications are still mostly unclear. Thus far only a small proportion of the genetic contribution to most studied conditions has been accounted for, and hundreds more SNPs remain to be identified.[12] Also, the genome-wide studies have mainly been in people of European origin, and other groups now need to be included.

The main impact of the new markers will probably be from the insights provided into disease mechanisms. Few of the new markers are expected to be useful in diagnosis. The ApoE ε4/ε4 variant, which was discovered 15 years ago, indicates a more than 14-fold risk of Alzheimer's disease in people of European origin.[13] As preventive interventions do not exist, debate has focused on diagnostic uses, but even this marker is generally seen as too weak for use in diagnosis.[14] Nevertheless, some patients may want testing—for example, filaggrin testing could provide an explanation for their allergies—even in the absence of diagnostic utility or specific treatment.

The new markers could improve risk prediction where effective preventive interventions are available. In coronary artery disease, for example, the SNP near p15/p16 has effects independent of the conventional risk factors,[6] so should provide additional information. Grouping all relevant SNPs into panels can identify groups of people at substantially higher or lower risks,[15] although most of the population tends to be somewhere in the middle. Much work is now needed to identify and evaluate each potential clinical application.

Conundrums

Although the work of translating discovery into evidence based practice is just beginning, several companies have

Information that should be supplied for genetic tests

- Specific purpose of the test (predicting a myocardial infarction occurring before age 70, for example)
- Target patient group (for example, is the test valid only for high risk families?)
- Analytic validity (accuracy of the DNA variant determination)
- Clinical validity (the evidence underpinning the disease prediction, for example)
- Clinical utility (evidence that the test can lead to changed clinical care and improved health)
- Ethical, social, and policy implications of taking the test (possible implications for family members, insurance, and employment, for example)
- Interpretation of the result (the absolute risk of the predicted outcome in the individual rather than in the general population, for example)
- Important areas of uncertainty (ethnic groups for whom evidence is lacking, interactions between classical and genetic risk factors, etc)

already marketed tests (table 2), many directly to the public. Predictive claims are common, but little information on precision or uncertainties is given. Recent media coverage on the genome-wide "tests" has described a US reporter counting the numbers of SNPs supposedly linked to major diseases.[16] In some tests, already discredited SNPs have remained in SNP panels.

Onlookers may view most of this activity as genetic astrology, producing entertaining horoscopes. Unfortunately, in areas such as pharmacogenetics misleading results could trigger erroneous treatment and involve major hazards. Recent reports that false negative Her2 overexpression testing in breast cancer led to women being denied specific treatment indicates the high stakes involved.[17] On the other hand, direct marketing of the BRCA1 and 2 familial breast cancer tests to women at low risk (for whom evidence of utility is lacking) was criticised for risking unfounded anxiety and unnecessary prophylactic surgery.[18] False reassurance from tests for common diseases could result in effective prevention measures, such as controlling weight and exercising, being ignored. Problems with insurance or implications for non-consenting family members may arise. Thus far it seems unlikely that these tests will be used in attempts to select low risk traits for babies, but this may emerge. Only time and monitoring will tell how common the potential hazards in polygenics will be.

What needs to change to ensure that tests are used appropriately?

Although some tests for single gene disorders have an aura of precision, the new genetic claims are clearly much less certain: only formal evaluation can provide an evidence base for clinical practice. The main policy imperative in genetic testing for common diseases should now be to ensure that good clinical evidence is generated and placed in the public domain. Preventing misleading claims should also be a priority.

Entering the genomics age with limited evidence or trust in the usefulness of markers is an uneasy position for clinicians. Not surprisingly, many feel unprepared[19] and look to laboratories to provide informative labelling.[20] The basic information needed on each test application (box) includes both laboratory ("assay") accuracy and the clinical meaning of the result for each patient. With access to such information (preferably over the internet), doctors and consumers would be better placed to use tests sensibly and safely. They could also help identify potential problems for regulators to review. Extraordinarily, European regulatory dossiers (including any clinical performance data volunteered) are currently kept secret, impeding informed decision making and risking safety.

In an age of evidence based medicine, the marketing of genetic tests with little evaluation is an unwelcome anomaly

Independent professional reviews of genetic markers are being set up, but these are generally limited to summarising available evidence. No authoritative source of reviews for clinicians on the new markers as clinical tests currently exists. Neither test makers, laboratories, nor clinicians have both the responsibility and the resources to undertake adequate clinical evaluation of most new tests, so data on clinical performance are scarce. As many markers are not patented and private investments in evaluating them therefore cannot be recouped, public funding alone or in partnership with the private sector will be needed. The resources required will often be modest in comparison for those needed for drug trials.

Statutory regulation of clinical tests is traditionally seen as focused on laboratory accuracy, although in both the United States and Europe oversight frameworks include clinical performance and ensuring the truthfulness of clinical claims. A key step for regulators is to identify the test applications that pose greater risks and need closer oversight. Criteria for classification of risk, long established in US regulation, focus on novelty (the lack of an approved similar test), a lack of supporting information (where decision making will be wholly dependent on the test result), and the impact on clinical management (whether the test result triggers risky interventions, for example). In many but not all cases, the new genetic markers will fall into midrange or higher risk levels on these criteria, especially if they are marketed directly to the public. Regulators in Canada, Australia, and the United States have placed genetic tests in these oversight categories—but in Europe virtually all are classified as low risk. As a result claims are not routinely reviewed before the tests are marketed, and European genetic test marketing is based on self certification. An independent scientific committee, including patient representatives, should be responsible for overseeing the risk categories for genetic tests, and the current European system of agreement between civil servants should end.

Better regulation would cover most clinical testing uniformly. At present, most laboratory developed tests are not scrutinised by the US Food and Drug Administration, introducing perverse incentives to market tests as services rather than (regulated) test devices. Similarly, the European regulatory system is interpreted by some as exempting "lifestyle"

Table 2 | Some laboratory developed common condition genetic tests offered direct to consumers

Company (base country)	Claimed prediction	Market
23andme (USA)	Whole genome scan: common diseases	USA
deCODE (Iceland)	Diabetes, atrial fibrillation, myocardial infarction	USA
deCODE (Iceland)	Whole genome scan: common diseases (deCODEme)	Global
GenoSense (Austria)	A range of common diseases	Europe, Canada, USA
Genetic Health (UK)	Offers GenoSense's tests	UK
Geneticom (Netherlands)	Range of common diseases	Europe
Genovations (USA)	Cardiovascular disease, osteoporosis	USA
Graceful Earth (USA)	Alzheimer's disease	USA
Interleukin (USA)	Heart disease	USA
Mygenome.com (USA)	Cardiovascular disease, osteoporosis, Alzheimer's	USA
Myriad (USA)	BRCA (breast cancer); Melaris (skin cancer)	USA, Europe
Navigenics (USA)	A range of common diseases	USA

Additional reading

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genetic testing and tests available through public sector laboratories, so both areas will need specific arrangements to ensure clinical quality.

The current limitations of statutory regulation may derive from the way the providers of diagnostic instruments and private laboratories operate. Although few laboratories currently provide genetic tests, large numbers could in the future, providing a challenge to regulation. Clinical evidence is complex, and universal standards can be defined only in broad terms. Some laboratories only want to report assay results, without making clinical claims (although current commercial genetic test services all make disease related claims). Given these structural difficulties, there has been disagreement on the appropriate scope of regulation, especially for laboratories that support doctors by carrying out established assays. Better regulation to ensure that clinical claims are reasonable, especially for novel genetic tests marketed directly to the public, deserves widespread support.

In an age of evidence based medicine, the marketing of genetic tests with little evaluation is an unwelcome anomaly. Unfortunately the harm of misleading tests tends to be hidden. The appearance of the tests for polygenic diseases provides a good opportunity to improve clinical test evaluation generally. Both consumers and professionals should push for a regulatory system that encourages clinical evaluation and makes the results (or lack of them) easily available to all. An authoritative database of reviews of the new markers as clinical tests is urgently needed. Professional bodies and health care providers should remind professionals that using tests in routine practice without evidence of utility is incompatible with good clinical practice. Reimbursers should support research but pay for routine use of tests only after they have been evaluated adequately. These improvements in the clinical evaluation of tests may prove as important as the discoveries themselves in realising the promise of genomics to improve health.

SUMMARY POINTS

Recent well designed studies have identified many new variants of common conditions, providing insights into mechanisms of disease

Most associations are modest, and hundreds more markers for most conditions remain undiscovered

Where effective interventions exist there may be some value in adding the new markers into risk prediction formulas, but each application needs clinical evaluation

Regulators should ensure easy access to all the relevant clinical evidence, especially for tests offered directly to consumers

We thank Timothy Frayling for comments on this paper.

Contributors and sources: All authors are co-investigators in a Wellcome Trust funded bioethics programme research project on the regulation of genetic tests for common conditions (report available at www.phgfoundation.org). Issues were explored through interviews and focus groups with stakeholders from academia, medicine, industry, and regulatory bodies. Fieldwork included over 80 stakeholders with input from senior US and European regulators. Analysis of issues discussed has informed this paper, but the synthesis is our own. DM leads genome-wide association studies for ageing related traits. All authors have contributed to themes discussed and had input into the manuscript. DM is guarantor.

Funding: The policy study informing this paper was funded by the Wellcome Trust bioethics programme, which played no part in the writing of this paper or the decision to submit it for publication. DM's genetic epidemiology programme is supported in part by US National Institutes of Health/National Institute on Aging (NIH/NIA) Grant R01 AG24233-01.

Competing interests: DM holds an unrestricted research grant from the BUPA Foundation.

Provenance and peer review: Not commissioned; externally peer reviewed.

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