Eye melanoma, media hype, and genomic medicine

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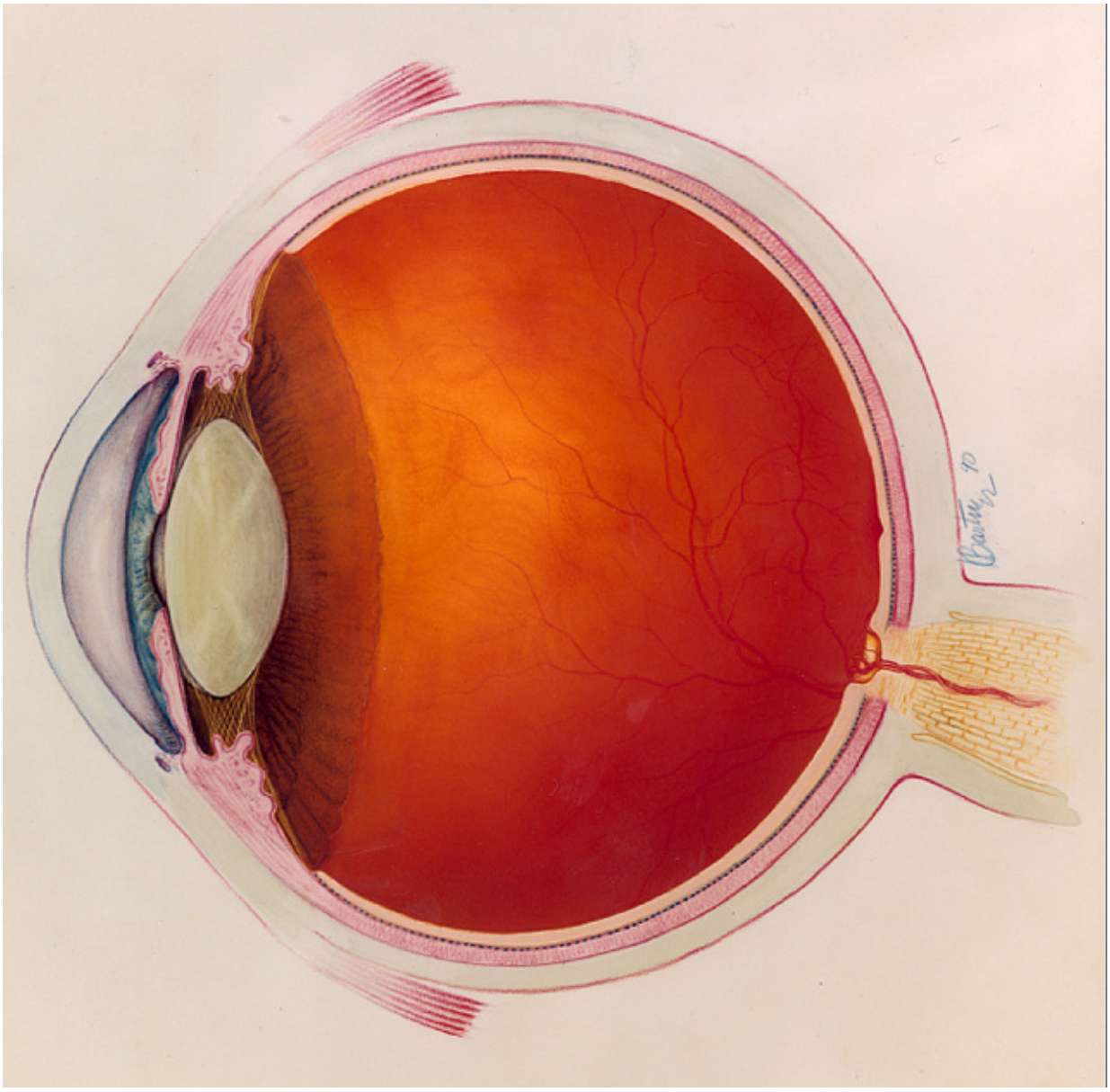

Melanoma of the eye presents a case study in the value of diagnosing by phenotype (symptoms and physical presentation) versus assessing risk genotype – a discussion that may impact ongoing efforts to sequence gazillions of human genomes. One recent estimate predicts two billion by 2025.

How much genome data will be clinically useful?

Uveal melanoma differs from the skin type

Cutaneous (skin) and uveal (eye) melanoma both begin in melanocytes. Uveal melanoma accounts for only 2.9% of all melanomas, with 2,500 cases diagnosed in the US annually. The uvea is the eye's pigmented middle layer, and about 83% of uveal melanomas are due to somatic mutations in two genes: GNA11 or GNAQ. Genetically speaking, the eye and skin cancers appear to be different diseases, despite arising in the same cell type.

The fact that 97.8% of all melanomas are in white people may suggest an underlying genetic susceptibility echoed through shared ancestry. When researchers recently surveyed results of several genome-wide association studies (GWAS), which tracked single-base signposts more common among people with skin melanoma or light pigmentation, the effort led to an obvious-in-retrospect suspect for uveal melanoma: the genes that impart eye color. The paper appears in the August 8 *Scientific Reports*.

Eye care specialists have long known that people with very light eyes are more likely to develop uveal melanoma than people with darker irises; here's a report from 2001. The condition is typically found during a

routine eye exam, but the first sign may be blurring of vision. The cancers originate in the iris, the ciliary body, or the choroid, with only those in the iris obvious from the outside. The others form at the back of the eye and are more likely to spread.

Narrowing down risk genes

Most cancers are the consequence of 2 mutational "hits" in a founding somatic (body) cell. A small percentage of cases are instead familial (aka germline), arising from a somatic mutation happening against a backdrop of an inherited cancer susceptibility mutation in every cell. The BRCA cancers are classic examples, and the 2-hit hypothesis of cancer was originally based on retinoblastoma. Online Mendelian Inheritance in Man reports that only 0.6% of uveal melanomas are familial, but that's based on studies with necessarily small samples for this rare cancer.

Familial uveal melanoma genes are BAP1, CDKN2A, and BRCA2. In contrast, for skin melanoma, the top implicated gene encodes the melanocortin-1 receptor (MC1R), which confers red hair, freckles, and pale skin and is notorious for making some Neanderthals redheads. MC1R mutations double the risk of melanoma even without sun exposure.

In the recent paper examining genetic underpinnings of uveal melanoma, Mohamed Abdel-Rahman, MD, PhD, of Ohio State University and Tomas Kirchhoff, PhD, of NYU and their colleagues considered 28 SNPs (single nucleotide polymorphisms) from past GWAS, seeking associations with skin melanoma or its known risk factors of light skin and eyes. They looked at 272 people with uveal melanoma and 1782 controls.

Light eyes are at higher risk of developing melanoma, but it is a rare cancer different from the skin variety.

Two genes behind eye color

Three of the SNPs were associated with uveal melanoma, and all are in the eye color genes. These risk variants would be inherited through the germline, and thereby confer susceptibility to the cancer even without sun exposure.

Eye color in humans is not quite as simple as the one-gene model of older textbooks. Two types of melanin pigments provide color, and nuances —light versus dark, clear blue versus greenish or hazel—arise from the distinctive peaks and valleys of the cellular topography at the

back of the iris, like the visual effect of a rough-textured canvas on paint. We all have about the same number of melanocytes in the eyes, but differ in the amount of pigment they produce. Most people have brown eyes; blue and green eyes are almost exclusively in people of European ancestry.

A gene on chromosome 15, OCA2, controls melanin synthesis. Delete it and albinism results. A recessive variant confers blue color and a dominant variant brown, but a nearby second gene, HERC2, controls expression of OCA2. Inheriting two recessive HERC2 variants abolishes control over OCA2, and blue eyes result.

Media coverage

The three identified SNPs are associated with raising risk of uveal melanoma by about 50%. That's not much, considering that the condition is extremely rare to begin with.

I turned to the media to see if anyone questioned the practical value of the new genetic data. The news release says "increased risk" without getting into statistics or even the magnitude of the elevated risk, yet quotes a researcher calling the findings likely to "provide a paradigm shift." The context is looking at pigmentation as a possible direct cause of cancer, rather than merely blocking ultraviolet radiation from the sun.

The first three media takes that google coughed up didn't mention the odds ratios that provide perspective, yet all include the "paradigm shift" quote. I think a hyperbolic quote with no interpretation of statistics is a pretty good definition of hype, suggesting perhaps a cyber aggregator at work rather than a set of human eyeballs actually reading the paper:

- Science Daily ran the news release unchanged.
- Genetic Engineering News used the sweeping headline "Eye

Color Determines Risk for Cancer" over the nearly verbatim news release.
- HealthNewsLine tacked a lovely lede onto the news release, but calls the study "one-of-a-kind." A round-up of existing association data to validate a known risk factor doesn't seem that original to me.

The bigger picture

The news release concludes with the possible use of the findings in preventing uveal melanoma, diagnosing it earlier, and targeting treatment. But it's hard to imagine a pharmaceutical company investing in a genetic test to identify a modest increase in risk for such a rare condition, already linked to light eye color, and already on the diagnostic radar of eye specialists.

So let's extrapolate to the rapidly accruing human genome data. How much of it will actually prove to be clinically useful? How many new genetic associations will circle back to what we already know from decades, centuries even, of observation? Will a marriage of bioinformatics and medical economics birth specialists who can identify data that can actually translate into improved risk assessment, diagnosis, and care?

My intent here is not to critique this particular study – it is elegant and interesting. But it may herald a redundancy in the types of information that we glean from human genome sequencing. Is sequence-as-many-as-we-can and store data the most sensible approach?

More information: Robert Ferguson et al. Genetic markers of pigmentation are novel risk loci for uveal melanoma, *Scientific Reports* (2016). DOI: 10.1038/srep31191