Criteria for evaluating genetic associations for use in direct-to-consumer personal genetic analysis

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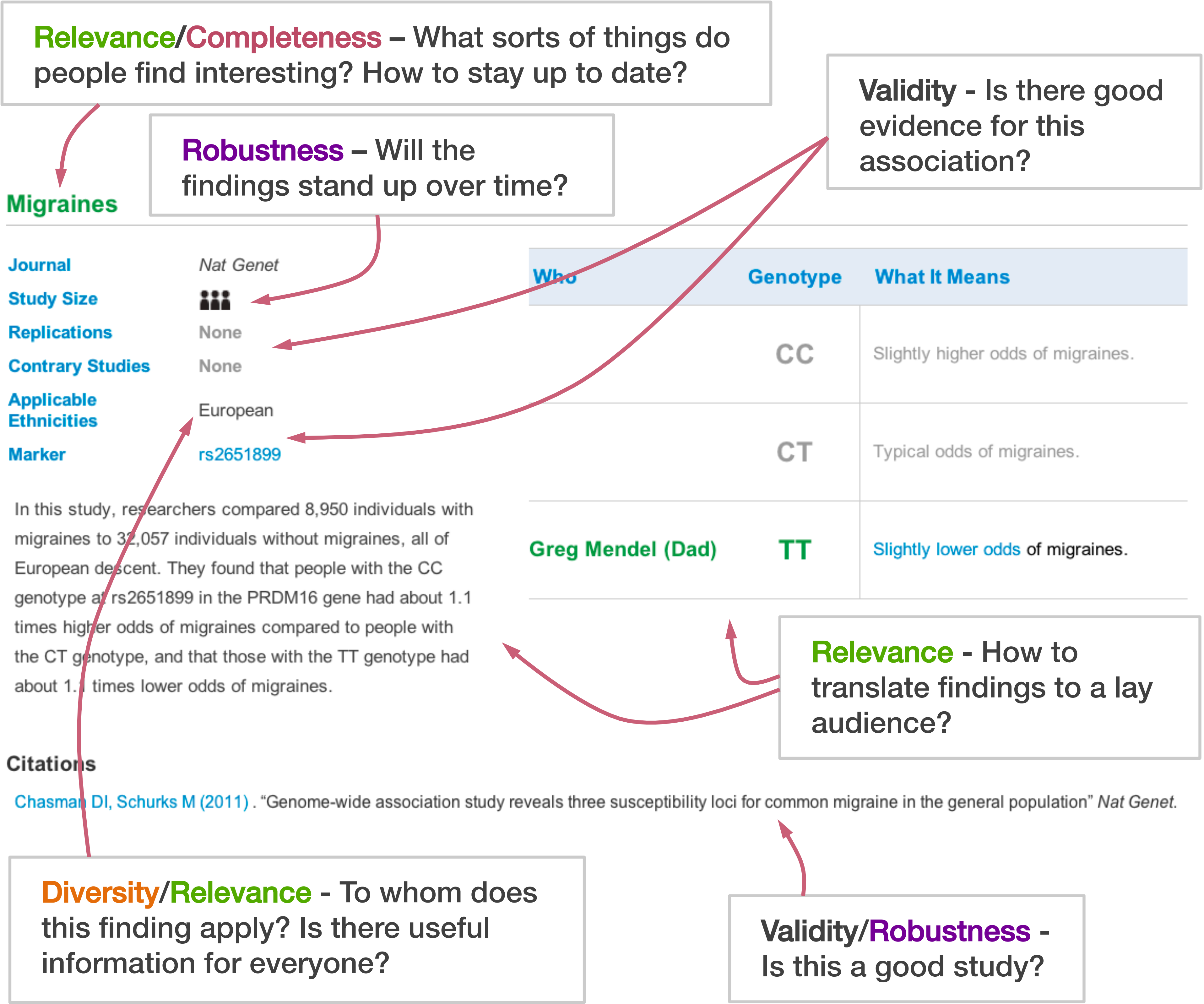
Introduction

Direct-to-consumer (DTC) personal genetics services link an individual's genetic data to various health conditions (such as disease risks, carrier status, and response to drugs) and physical traits (e.g. hair color, eye color). These companies make connections based on findings published in the scientific literature but which conditions, studies and specific findings to include can still vary between companies depending on their specific critieria and goals.

These differences – and the consequent differences in results provided by different companies for the same diseases for the same individual[1,2] – have played a large role in the public's confusion and skepticism regarding personal genetics, as illustrated by articles published in scientific journals[3] and the popular press and epitomized by an "exposé" of the industry released by the U.S. Government Accountability Office[4] in July of 2010. This presentation describes 23andMe's considerations in this area.

23andMe Considerations

Validity	Robustness	Completeness
	Relevance	Diversity



Relevance/**Completeness** – What sorts of things do people find interesting? How to stay up to date?

Robustness – Will the findings stand up over time?

Validity - Is there good evidence for this association?

Migraines

Journal *Nat Genet*
Study Size
Replications None
Contrary Studies None
Applicable Ethnicities European
Marker rs2651899

In this study, researchers compared 8,950 individuals with migraines to 32,057 individuals without migraines, all of European descent. They found that people with the CC genotype at rs2651899 in the PRDM16 gene had about 1.1 times higher odds of migraines compared to people with the CT genotype, and that those with the TT genotype had about 1.1 times lower odds of migraines.

Who	Genotype	What It Means
	CC	Slightly higher odds of migraines.
	CT	Typical odds of migraines.
Greg Mendel (Dad)	TT	Slightly lower odds of migraines.

Relevance - How to translate findings to a lay audience?

Citations

Chasman DI, Schurks M (2011) . "Genome-wide association study reveals three susceptibility loci for common migraine in the general population" *Nat Genet.*

Diversity/**Relevance** - To whom does this finding apply? Is there useful information for everyone?

Validity/**Robustness** - Is this a good study?

- 🟣⚪ **Associations must be statistically significant** (p-value is genome-wide significant ($< 5\times10^{-8}$) or < 0.01 after Bonferroni correction).
- 🟣⚪ **Study findings should be free from or account for common sources of bias** (such as population stratification).
- 🟣 **Use study size as a proxy for confidence in an association** (750+ cases preferred).
- 🟢🔴🟠 **Report on associations with varying levels of evidence**, as long as they meet the **validity criteria** above and limitations are indicated. Associations with the highest level of evidence are considered **Established**, and associations that meet minimum criteria are **Preliminary**.
- 🟣 **Associations must be independently replicated** by different research groups in large studies (750+ cases) to be considered Established. (Associations identified by large consortia are also considered Established.)
- 🟢🟠 **Report on associations for conditions and traits that are of broad interest.**
- 🔴🟠 **Provide information to populations that are underrepresented in research.**
- 🟢🟣⚪ **Associations apply only to the population in which they are found** (e.g. European, Asian, African).
- 🔴🟢 **Evaluate new research and update information** provided to users on a regular basis.

Summary

As a research-oriented company that values transparency, 23andMe has always made public its rules and rationale for reporting on genetic associations published in the literature.[5] 23andMe aims to balance diversity, completeness, robustness, and relevance in the information it provides to users, without sacrificing scientific validity. The criteria described here address this set of considerations and enable 23andMe to make measured decisions regarding the reporting of genetic associations.

References

1. Barlow-Stewart K, Cormick C. "Consistently inconsistent – DTC results of identical twins from three companies and implications for service provision. Presented at ICHG/ASHG, Montreal, October 2011; 1350F.
2. Kido T, et al. "Comparisons of disease risk assessment of direct consumer genetic services for Japanese individuals. Presented at ICGH/ASHG, Montreal, October 2011; 1385T.
3. Ng PC, Murray SS, Levy S, Venter JC. (2009) "An agenda for personalized medicine." Nature. 461:724-726.
4. U.S. Government Accountability Office. "Direct-To-Consumer Genetic Tests: Misleading Test Results Are Further Complicated By Deceptive Marketing and Other Questionable Practices." July 22, 2010. http://www.gao.gov/products/GAO-10-847T.
5. Wu S, Naughton BT. "Guidelines for vetting genetic associations." https://www.23andme.com/for/scientists. 23andMe white paper, updated August 25, 2011.