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Genetic Ancestry Testing What Is It and Why Is It Important?

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Genetic ancestry testing. in which genetic data are used to estimate the geographic origins of a person's recent ancestors, has grown rapidly in popularity. A recent estimate indicates that more than 26 million people worldwide have undergone genetic

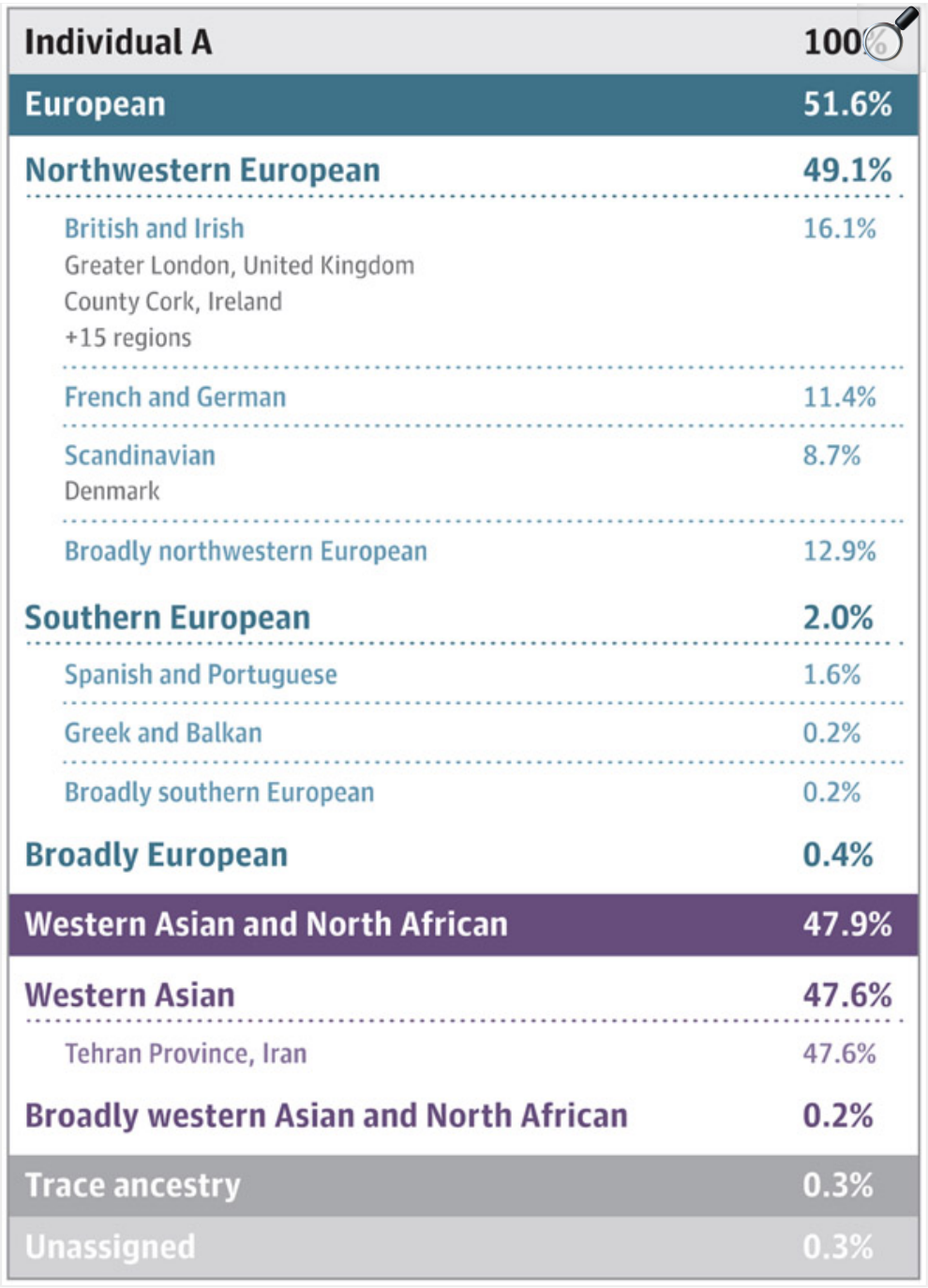
ancestry testing by direct-to-consumer (DTC) companies.[1] These tests provide information about an individual's ancestral roots, and they can help to connect people with their relatives, sometimes as distantly related as fourth or fifth cousins. Such information can be particularly useful when a person does not know their genealogical ancestry (eg. many adoptees and the descendants of forced migrants). Increasingly and not without controversy, genetic ancestry testing is being used beyond its original purpose, for example, to help identify or exclude criminal suspects.[2] In the clinical setting, persons may share their ancestry test results with their clinician with the expectation that the results will inform health care decisions.

How It Works

Genetic ancestry testing involves the comparison of a large number of DNA variants measured in an individual with the frequencies of these variants in reference populations sampled from across the world. The geographic region in which an individual variant has its highest frequency is assumed to be the most likely location of an ancestor who transmitted the variant to the person being tested. Ancestry testing is traditionally done for mitochondrial DNA (transmitted only by females and reflecting the origin of 1 maternal ancestor) and for Y chromosome DNA (transmitted only from father to son and reflecting the origin of 1 paternal ancestor). A more comprehensive assessment of ancestry can be conducted by assaying a half million or more autosomal variants (single-nucleotide variants [SNVs]; formerly single-nucleotide polymorphisms [SNPs]). which are inherited from both parents. Most commonly, these SNVs are assayed using a DNA microarray, but DNA sequence data can also be used. For autosomal testing, it is common to portray the most likely geographic origin of a group of SNVs located within a

chromosome segment (eg, *ancestry painting*) (Figure).[3] By counting the percentage of SNVs originating from each geographic region, the percentage of an individual's ancestry derived from each region can be estimated.

Figure. Estimates of Ancestry Composition.



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Breakdown of estimated percentages of ancestry from different worldwide populations ranked from highest to lowest and from continental to regional levels for one of the authors. Illustration adapted from results reported by 23andMe.

Ancestry can be designated very broadly (eg, western Asian, southern European) or as finely as by regions within individual countries. In the latter case, accuracy is likely to decrease, and some DTC companies allow the user correspondingly to adjust the degree of speculation in ancestral estimation. In all cases, accuracy is strongly affected by the choice of reference populations and the selection and number of SNVs, all of which vary among ancestry testing companies. Consequently, it is not unusual for different companies to report somewhat different ancestral profiles for the same DNA sample.[4] Furthermore, many human populations have migrated considerably during their history[5]; therefore, modern-day samples represent a static and potentially inaccurate portrayal of a region's inhabitants in the past. Even the term *ancestry* is subject to a variety of interpretations and can be based on geographic, historical, cultural, or religious definitions.[6] For these reasons, there is considerable room for error or ambiguity in inferring and interpreting a person's genetic ancestry. Nonetheless, some studies have shown concordance between self-reported and genetically estimated ancestry.[7]

Important Clinical Care Considerations

Knowledge of a person's ancestry can be important because the frequencies of genetic risk variants sometimes vary with ancestry, although most such risk variants are not assayed directly by ancestry tests. However, some DTC ancestry testing companies provide health reports in which they directly test a limited number of DNA variants associated with conditions such as breast cancer and Alzheimer disease or less common genetic conditions such as cystic fibrosis, polycystic kidney disease, and various

inborn errors of metabolism (the latter enabling identification of carrier status).

In most genetic research studies of health and disease, ancestry information has replaced the use of racial categories. Because of its increased accuracy in comparison with self-reported ancestry, genetically estimated ancestry can improve statistical power to detect genetic risk factors for common diseases in genome-wide association studies.[8] Often such risk factors vary by ancestry, and the cumulative disease risk aggregated across multiple DNA variants (ie, the polygenic risk score) appears to be highly sensitive to differences in ancestry.[9] Accordingly, if the clinical utility of polygenic risk scores is eventually established, ancestry information could be important for accurate interpretation of risk. Moreover, because the great majority of genetic studies have been done in populations of European ancestry, the pathogenicity of rare variants is more difficult to assess in persons of predominantly non-European ancestry. Ancestry information can thus help to avoid misinterpretation of genetic tests.

Ancestry testing also can yield unanticipated results such as lack of expected ancestry or the presence of unexpected ancestry. Discordance between pairs of siblings or between father and child can reveal nonpaternity, which is estimated to occur in approximately1% to 2% of births in Western populations.[10] Large identical regions of DNA on both chromosomes in a tested individual can identify parental consanguinity. These results could have significant psychosocial impacts.

Value

Ancestry information has interpretive value in both clinical and research settings, and provides more accurate and personalized

information about a patient's genetic heritage than do broad categories like race or ethnicity. For example, in a self-identified African American patient with recurrent respiratory infections, ancestry testing could reveal that both copies of the *CFTR* gene are likely to have a European origin, increasing the relative likelihood of a diagnosis of cystic fibrosis. Although DTC ancestry testing does not predict an individual's future health, it is relatively inexpensive (approximately $100) and widely available. If DTC delivery of health-related genetic test results gains acceptance, it is likely that ancestry testing companies will add more variants of medical relevance to their platforms, and clinicians will be expected to understand and explain these results.

Evidence Base

The authors are aware of no clinical care guidelines regarding ancestry testing. In a clinical setting, ancestry information can be helpful for selecting the most appropriate genetic test (eg, for rare genetic conditions), interpreting genetic test results, and assessing risk for common diseases. However, associations between ancestry and disease are indirect, and measurement of ancestry is subject to error. Ancestry testing is unlikely to become part of routine clinical care of any major medical specialty, particularly if risk variants can be tested directly, as is expected with advances in precision medicine.

Bottom Line

Genetic ancestry testing can provide insights on the geographic origins of an individual's ancestors, as well as some information that can aid in assessment of risk for some heritable conditions. The accuracy of testing is limited by the migrations and mixing of

populations over time. Unexpected findings regarding ancestral origins and family relationships can have psychosocial consequences.

Footnotes

Conflict of Interest Disclosures: None reported.

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