Towards diversity in asthma pharmacogenetics

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Published in:
Lancet child & adolescent health

DOI:
10.1016/S2352-4642(21)00330-8

Publication date:
2021

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Published Online
November 8, 2021
https://doi.org/10.1016/
S2352-4642(21)00330-8

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Asthma is the most common chronic disease in children, and it disproportionally affects children from non-White minorities. A meta-analysis of 13 studies from the UK reported a higher frequency of clinician-diagnosed asthma in Black (15·0%), compared with White (10·6%) and south Asian children (7·6%).[1] In the USA, Black children with asthma have higher rates of emergency department visits, hospitalisations, and asthma-related deaths compared with White children.[2]

Many factors might contribute to a high prevalence of asthma in minority groups, such as poor housing quality, high exposure to allergens, tobacco smoke, air pollution, and suboptimal access to health care.[3] Under-prescription or lower adherence to long-term controller medications, or both, and over-reliance on emergency care[4] puts minority populations at risk for asthma exacerbations. Even after correcting for socioeconomic factors and medication use, Black children with severe or difficult-to-treat asthma have worse asthma outcomes compared with White children.[5] Why these children have different treatment responses has not been unravelled; it might have a genetic basis.

Over the past 15 years, genetic studies have provided an improved understanding of genetic variation contributing to asthma[6] as well as to asthma treatment response.[7] However, people of African descent were strongly under-represented in genetic studies. Worldwide, of all genome-wide association studies (GWASs) summarised in the GWAS Catalogue until 2018, only 2% of participants had African ancestry.[8] Fortunately, the scientific community has recognised the need to investigate populations of non-European descent. Although all humans are highly genetically identical (>99·99%), the between and within population genetic variance of African populations is much higher than other populations because of their long evolutionary histories, which calls for genetic studies in populations of African descent.

For the **GWAS Catalogue** see www.ebi.ac.uk/gwas

In *The Lancet Child & Adolescent Health*, Victor E Ortega and colleagues investigated the pharmacogenetics of treatment response in patients of African descent with asthma participating in the Best African Response to Drug (BARD) trials.[9] These patients had poor asthma control while on low-dose inhaled corticosteroids (ICSs). Four different step-up regimens were compared: doubling or quintupling ICS dosages, and low-dose or high-dose ICS combined with a long-acting beta agonist (LABA). These treatments were compared using a hierarchical composite score that sequentially evaluated asthma exacerbations, asthma-control days, and lung function after 14 weeks of treatment. The trial in children aged 5–11 years showed an equal percentage of children with a superior response to quintupled ICS dose as with the doubled ICS–LABA combination (both 46%). By contrast, the trial in adolescents and adults (aged 12–69 years) showed a higher percentage of patients with a superior response to the doubled ICS–LABA combination (53%) compared with quintupled ICS dose (27%). This age effect is remarkable, and could be due to inclusion of more heterogeneous phenotypes of asthma in the adolescent and adult trial (218 of 267 participants were adults) or more adverse events of LABA in the 5–11 year age group, as previously reported.[10] These observations illustrate that extrapolation of treatment effects in adolescents and adults to school-aged children is not justified; separate studies in this age group are needed.

In the BARD trials, global African ancestry was not associated with treatment response.[11] However, specific loci differentially inherited among individuals of African ancestry could still have pharmacogenetic effects. This follow-up study used inferred local ancestry to test the association of the number of copies from African ancestry in each genomic position with treatment responses.[9] In children, a novel locus on chromosome 12 was associated with superior responsiveness to quintupled ICS dose compared with low-dose ICS plus LABA. In adolescents and adults, a novel locus on chromosome 6 was associated with superior responsiveness to quintupled ICS dose versus doubled ICS dose.

The publication of Ortega and colleagues' study marks a step forward in our understanding of the pharmacogenetics of asthma in patients of African ancestry. Although the initial power to identify significant findings was not high, evidence of replication of two loci in independent populations was provided. We propose that future, larger studies should prospectively confirm the importance of these genetic variants. After this, these variants await further functional genetic studies. What genes do they regulate? How do these genes interact with asthma treatments? Do these genes

encode a target for intervention? Again, samples from patients of African descent are under-represented in databases that report the functional effects of genetic variation. Thus, future functional studies also need to prioritise inclusion of minority populations.

Replication and validation of these loci might not only benefit patients of African ancestry, but serve the broader patient community: genetically validated drug targets have a two-fold higher chance of successful drug development;[6] and drugs developed on the basis of information in one population might be efficacious in other populations.

In conclusion, the work presented by Ortega and colleagues illustrates the many reasons to be inclusive in future pharmacogenetic research. This is the way forward.

We declare no competing interests.

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Shifting stigma about autistic young people

Who do you think of when autism is mentioned? Maybe a familiar trope comes to mind: an eccentric white man, perhaps in the vein of *The Big Bang Theory*'s socially naive genius, Dr Sheldon Cooper, or savant Raymond Babbitt of *Rain Man* fame. As endearing as they may be, characters like these reflect outdated and stereotypical understandings of autism that can have harmful consequences for autistic young people. For many autistic people, these stereotypes and the stigma that they reinforce might be a greater barrier to wellbeing than the characteristics of autism itself, with particular implications for children and adolescents.[1]

Link and Phelan[2] define stigma as comprising four components: labelling of human differences; associating labelled groups with negative stereotypes; separating labelled groups from the majority in an "us" and "them" dynamic; and status loss and discrimination against labelled groups. Importantly, stigmatisation can only occur within the context of a social power imbalance. To enact stigma, a dominant group ("us") must hold enough power to engage in individual or structural discrimination against a labelled group ("them").

Autistic people are vulnerable to each of the four component processes by which stigmatisation occurs,[1] and research to date has found considerable evidence of the stigmatisation of autistic people and their families. For example, parents of autistic children consistently report that they and their children are subject to negative stereotyping and judgement, social isolation and rejection, and discrimination.[3] Non-autistic people can hold dehumanising attitudes, viewing autistic people as child-like, even though autistic children inevitably grow up to become autistic adults.[4] Non-autistic people are less willing to engage socially with autistic people than with non-autistic people, and can make negative judgements about autistic children and adults after just seconds of exposure.[5]

Unsurprisingly, the experience of stigmatisation can have considerable negative effects for autistic people. Exposure to stigmatising events, repeated rejection, and discrimination can result in internalised stigma:[1] the process of applying negative societal beliefs to one's personal identity. This type of stigma has been described as the most insidious form of minority stress


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Published **Online**
September 30, 2021
https://doi.org/10.1016/S2352-4642(21)00309-6