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Evidence for and against genetic testing to identify children at risk of high myopia

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Commentary

In the current issue, Yanxian Chen et al.[1] improve our understanding of the accuracy with which clinicians can identify children destined to develop high myopia. Given the high heritability of refractive error, it may come as a surprise that they find genetic testing does not improve prediction beyond that obtainable from cycloplegic autorefraction. Their study has implications for clinical practice.

Myopic maculopathy and other pathological changes associated with myopia are a frequent cause of visual impairment, especially in East and Southeast Asia.[2] The risk of maculopathy increases with the degree of myopia.[3] Randomized controlled trials have demonstrate that childhood myopia progression can be slowed by 40-50% – at least over the 2 to 3 years that such trials have been run, prompting the adoption of treatment interventions for myopia in both the East and West.[4] This growing trend towards early intervention for myopia raises a number of questions: Can such treatment actually prevent high myopia, as opposed to slowing its onset? What is the most effective form of treatment? And crucially - which children should be treated and at what age?

It is this last question that Chen et al.[1] addressed, studying data from the Guangzhou Twins Eye Study (GTES) of refractive development. GTES followed approximately 1200 twins aged 7-15 years-old at baseline. Refractive error was assessed by cycloplegic autorefraction, and most participants attended annual follow-up visits (60% attended 6 or more assessment visits). The authors developed a statistical model to predict the development of high myopia using information about the child's age, gender and baseline refractive error. In an independent sample of GTES participants who had been omitted from the model-building process, a so-called "validation set," prediction accuracy was outstanding: area under the receiver operating characteristics curve (AUROC) was 0.95. Performance was even better (AUROC = 0.98) when information available from one or more follow-up visits was incorporated.

Notably, the model's performance in predicting high myopia was *not* improved if genetic information was added to the mix. Specifically, the authors assessed whether prediction accuracy was enhanced by including a 'polygenic risk score' as a predictor variable (derived using 135 genetic variants from a large genome-wide association study for refractive error[5]). The main reason for the lack of improvement from the addition of the polygenic risk score is likely that the impact of genetic variants will already be evident in the cycloplegic refraction of the children, either at baseline or at follow-up visits. Reduced accuracy (typically of the order of 40%) in East Asians for a polygenic risk score derived in Europeans, may also have contributed.

Therefore, has genetic testing nothing to offer clinicians interested in identifying children most at risk of high myopia? At this year's ARVO conference we presented work (Ghorbani Mojarrad et al. ARVO E-abstract E4816) seeking to address whether genetic information was predictive of high myopia when no other information was available, for example in early childhood or in utero. The best performance was obtained using a polygenic risk score derived from over a million genetic variants: AUROC = 0.73, i.e. midway between pure chance and perfect prediction.

While greatly inferior in performance to the model reported by Chen et al.[1] (AUROC = 0.73 vs. 0.95), we found individuals with a polygenic risk score in the top 10% were at 6-fold higher risk of high myopia compared to the 90% of individuals with lower scores. Thus, for very young children whose cycloplegic autorefraction may not yet be indicative of their risk of high myopia, genetic testing could identify those who would benefit from careful monitoring and encouragement to spend more time outdoors.[4] For many conditions there is a latent period when interventions can be effective in reducing later risk, before the disease or trait has become evident. Clinically we can now ask: Is there a latent period for myopia and can genetics help us to identify children destined for high myopia at this early stage? Once children are about 10 years-old or so, the new findings by Chen at al. strongly support the use of cycloplegic autorefraction (with no need for additional genetic tests) to identify those with myopia, or progressing towards myopia, who would benefit most from treatment to slow progression.

References (up to 5)

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