technologies such as long-read sequencing approaches[7]. A substantial proportion of people who currently lack a genetic diagnosis could receive one through the application of these newer methods. In time, polygenic scores could become an absolute necessity for medical genetics.

Huang and colleagues also investigated the mechanisms by which polygenic scores influence neurodevelopmental conditions. To do this, the researchers applied a method called the polygenic transmission disequilibrium test[8] to estimate whether individuals with a rare neurodevelopmental condition but without a genetic diagnosis inherit a disproportionate amount of common-variant disease risk from their unaffected parents. The authors found evidence that suggests there is disproportionately high transmission of the polygenic risk for rare neurodevelopmental conditions from unaffected parents to children. This effect was large and statistically significant in families with affected female children, but it was not detected in families with affected male children.

However, this transmission is complex: although polygenic risk for rare neurodevelopmental conditions can be directly inherited by offspring[9], polygenic scores for traits such as educational attainment and cognitive performance showed no direct genetic effects on the children. Instead, genetic variants for these traits that were present in the parents but not transmitted to the child correlated with the child's risk of developing a neurodevelopmental condition. This suggests that parental genetic background might exert an indirect genetic effect, possibly through parental behaviour or the family environment. It should be emphasized, however, that this type of indirect effect might be specific to educational attainment and cognitive traits, and not relevant to other traits[10,11].

An analysis of particular interest was the examination of how genetic effects are shared between neurodevelopmental and psychiatric conditions. Because there are complex relationships between psychiatric conditions and educational attainment[12], Huang *et al.* adjusted for the effects of the genetics of cognitive performance and educational attainment for each psychiatric condition that they analysed. Their results confirm that there is a moderate genetic correlation between rare developmental conditions and schizophrenia. They also found that the apparent genetic correlation between neurodevelopmental conditions and attention-deficit hyperactivity disorder (ADHD) disappears after adjustment for educational attainment. These results are interesting, strongly confirming known links for schizophrenia[13], but not confirming what researchers thought they knew about ADHD[14]. After correcting for educational attainment, the authors also found genetic correlations that suggest that there could be a neurodevelopmental basis for anorexia nervosa and bipolar disorder, a finding that on the surface might be surprising, but is consistent with clinical findings for these conditions[15,16].

The authors make commendable efforts to explain their findings by including a 'frequently asked questions' document, which they developed with an engagement panel comprised of members of the public and study participants. This means that their study is particularly accessible to families and clinicians who might not be familiar with the complex genetic epidemiology methods that Huang and colleagues use.

> **"In time, polygenic scores could become an absolute necessity for medical genetics."**

This study represents a meaningful step forwards in understanding the genetic basis of rare neurodevelopmental conditions. By shedding light on the contribution of common genetic variants, especially for people who do not yet have a genetic diagnosis, this research has the potential to improve the lives of individuals and families affected by these conditions. The findings also highlight the urgent need to consider both rare and common genetic variants in genetic research, diagnosis and treatment of neurodevelopmental and other rare and complex conditions.

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Astronomy

Distant sparkles hint at how the Milky Way formed

Brian Welch

The JWST has captured images of the Firefly Sparkle — a galaxy that resembles an early Milky Way — in the process of being assembled from star clusters. The discovery could help to reveal how the Milky Way formed in the early Universe. **See p.332**

The Milky Way formed around 13.5 billion years ago, but it's not possible to travel back in time to see exactly how it happened. Studies of the Galaxy's ancient stars[1] offer some clues, as do simulations[2], but the observable light from our cosmic home was emitted too recently to enable astronomers to examine its beginnings directly. One way around this problem is to study other galaxies that resemble the Milky Way. On page 332, Mowla *et al.*[3] used observations from the James Webb Space Telescope (JWST) to investigate a distant galaxy with a mass that matches the expected mass of the Milky Way shortly after its formation in the early Universe.

When astronomers observe distant galaxies, they see light that was emitted billions of years ago, because it takes time for light to travel across space to their telescopes. Earth's separation from such far-away galaxies, and thus how long ago their light was emitted, can be measured, thanks to the constant expansion of the Universe. As light journeys across the cosmos, its wavelength is stretched along with the expanding fabric of space, making it seem redder than it was when it was emitted. This is known as cosmological redshift, and the change in the wavelength is related to the distance the light travels and the age of the Universe at the time of emission.

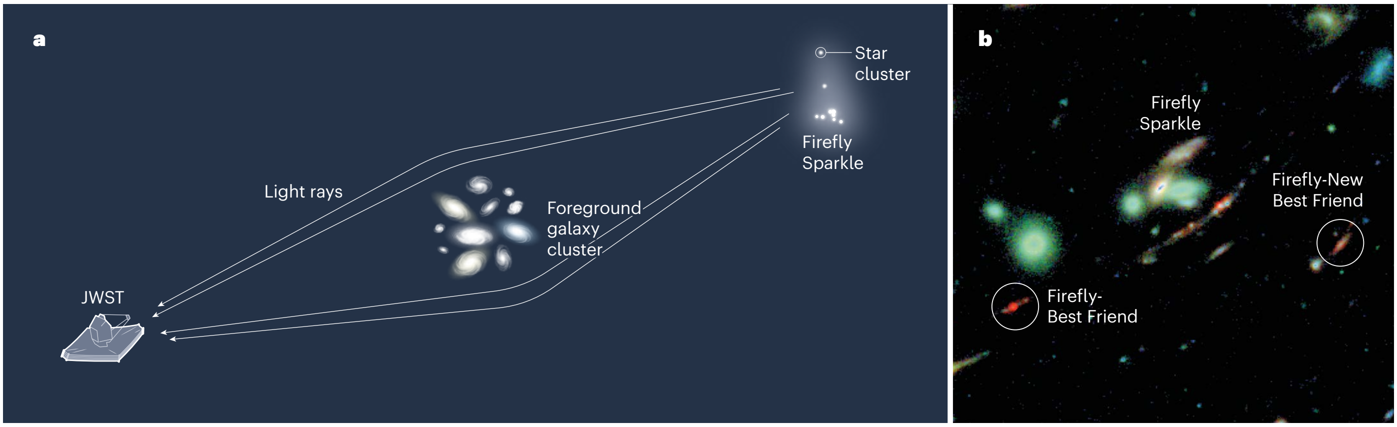

Figure 1 | A magnified view of a galaxy forming in the early Universe. a, Mowla *et al.*[3] measured the physical properties of a galaxy known as the Firefly Sparkle, as well as those of its star clusters, using a magnification effect called gravitational lensing, in which a large object in the foreground bends the path of light between a distant source and an observer. The Firefly Sparkle has a mass similar to that predicted for the early Milky Way, so the team's observations provide a glimpse at what the formation of the Milky Way might have looked like. **b**, The authors' images were obtained using the James Webb Space Telescope (JWST), which was also able to resolve a pair of neighbouring galaxies that the authors have named the Firefly-Best Friend and the Firefly-New Best Friend.

The most precise way to measure redshift is spectroscopically, by comparing the measured wavelength of a certain spectral feature of the light with the wavelength at which the light is known to have been emitted. Mowla *et al.* trained the JWST on a galaxy whimsically known as the Firefly Sparkle, and measured a spectroscopic redshift of 8.296, which means that the galaxy was formed in the first 600 million years of the Universe.

Although JWST observations have pinpointed many galaxies with redshifts of 8 and beyond, typically only the brightest of these galaxies can be observed, because the vast distances dim the light. It is also often impossible to determine the underlying structure of these distant galaxies, because their small-scale features blend together — even in the high-resolution images taken by the telescope.

In the case of the Firefly Sparkle, Mowla *et al.* were able to circumvent these challenges thanks to a phenomenon called gravitational lensing, which occurs when massive foreground structures warp the path of light between an astrophysical object and its observer (Fig. 1a). The effect of this distorted path is that the background object seems enlarged, as if it were being viewed through a cosmic magnifying glass. A massive cluster of galaxies lies between the Firefly Sparkle and Earth; Mowla *et al.* were therefore able to measure tiny, faint features of the galaxy, which would have been difficult or impossible to detect in an unlensed galaxy.

The Firefly Sparkle is smaller and fainter than many other galaxies observed from a similar epoch. Mowla *et al.* found that the mass of all the stars in this galaxy is around ten million times that of the Sun, making it one of the lowest-mass galaxies in the early Universe observed so far. Intriguingly, this mass is consistent with simulations of Milky Way analogues at this early time, hinting that the Firefly Sparkle might have grown into a galaxy similar to our own.

The authors also identified a pair of neighbour galaxies with the same redshift as the Firefly Sparkle, which they dub the Firefly-Best Friend and Firefly-New Best Friend (Fig. 1b). For galaxies, as for people, it is important to have friends. These 'best friend' galaxies are located 2 kiloparsecs and 13 kiloparsecs, respectively from the centre of the Firefly Sparkle; these distances are less than the radius of the Milky Way, which is 15 kiloparsecs. Although the fate of the Firefly and its friends cannot be determined from the data, studying these possible Milky Way progenitors can provide clues as to how the Milky Way formed.

"Studying these possible Milky Way progenitors can provide clues as to how our own Galaxy formed."

Many small, highly magnified star clusters are visible in the Firefly Sparkle. These star clusters are compact and dense, with surface mass densities greater than those seen in either old globular clusters or young star clusters in the Milky Way. These sparkles in the Firefly galaxy are not the most distant or densest star clusters observed (that record currently belongs to the Cosmic Gems[4]). However, they are the most distant star clusters that have been resolved with spectroscopic data so far, and this exquisite resolution enabled Mowla *et al.* to investigate these sparkles in great detail. Their spectra show evidence of a high gas temperature, which is unusual for star-forming regions and indicates that a powerful source is pumping a large amount of energy into the gas.

By considering this high temperature, and by modelling the full spectrum of the galaxy's stellar population, the authors argue that, when the observed light was emitted, the Firefly Sparkle was forming more high-mass stars than would be expected from conventional star-formation models. This indicates that its stars might have formed in extreme environments. Although this finding would offer insight into how the Milky Way formed, and into the general physics of star formation in the early Universe, there are a few caveats to the measurement presented by Mowla and colleagues.

The spectra were taken with a low-resolution mode of the JWST, so some of the key emission lines are blended together and therefore have considerable uncertainty. The spectra also include contributions from four star clusters near the centre of the galaxy, as well as from the diffuse light of the Firefly Sparkle, making it impossible to distinguish which sources contribute to each spectral feature.

Mowla and colleagues' detailed study of magnified star clusters provides tantalizing clues about the formation mechanisms for galaxies such as the Milky Way. Using the JWST to perform spectroscopy with even higher spatial and spectral resolution would improve astronomers' confidence in the measured properties of the Firefly Sparkle. Meanwhile, further discoveries and detailed spectroscopic observations of highly magnified galaxies in the early Universe will help to answer the question of how the first galaxies formed.

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