x-y, *x-z*, and *y-z* cross sections of the cell (Fig. 2, C to E, and movie S1) (*27*).

To characterize our cell imaging resolution more quantitatively, we identified point-like objects in the cell that appeared as small clusters of localizations away from any discernible microtubule filaments. These clusters likely represent individual antibodies nonspecifically attached to the cell. The FWHM values of these clusters, which were randomly chosen over the entire measured *z*-range of the cell, were 22 nm in *x*, 28 nm in *y*, and 55 nm in *z* (fig. S2) (*27*), similar to those determined for individual molecules immobilized on a glass surface (compare fig. S2 with Fig. 1C). Two microtubule filaments separated by 100 nm in *z* appeared well separated in the 3D STORM image (Fig. 2F). The apparent width of the microtubule filaments in the *z* dimension was 66 nm, slightly larger than our intrinsic imaging resolution in *z* and in quantitative agreement with the convolution of the imaging resolution and the independently measured width of the antibody-coated microtubule (Fig. 2F). Because the effective resolution is determined by a combination of the intrinsic imaging resolution (as characterized above) and the size of the labels (e.g., antibodies), improved resolution may be achieved by using direct immunofluorescence to remove one layer of antibody labeling, as we show in the next example, or by using Fab fragments or genetically encoded peptide tags (*29*, *30*) in place of antibodies.

Finally, to demonstrate that 3D STORM can resolve the 3D morphology of nanoscopic structures in cells, we imaged clathrin-coated pits (CCPs) in BS-C-1 cells. CCPs are spherical cage-like structures, about 150 to 200 nm in size, assembled from clathrin and cofactors on the cytoplasmic side of the cell membrane to facilitate endocytosis (*31*). To image CCPs, we adopted a direct immunofluorescence scheme using primary antibodies against clathrin doubly labeled with Cy3 and Alexa 647 (*27*). When imaged by conventional fluorescence microscopy, all CCPs appeared as nearly diffraction-limited spots with no discernible structure (Fig. 3A). In 2D STORM images in which the *z*-dimension information was discarded, the round shape of CCPs was clearly seen (Fig. 3, B and D). The size distribution of CCPs measured from the 2D projection image, 180 ± 40 nm, agrees quantitatively with the size distribution determined using electron microscopy (EM) (*32*). Including the *z*-dimension information allowed us to clearly visualize the 3D structure of the pits (Fig. 3, C and E to H). Figures 3C and 3E show the *x-y* cross sections of the image, taken from a region near the opening of the pits at the cell surface. The circular ring-like structure of the pit periphery was unambiguously resolved. Consecutive *x-y* and *x-z* cross sections of the pits (Fig. 3, F to H) clearly revealed the half-spherical cage-like morphology of these nanoscopic structures that was not observable in the 2D images. These experiments demonstrate the ability of 3D STORM to resolve nanoscopic features of cellular structures with molecular specificity under ambient conditions.

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An Association Between the Kinship and Fertility of Human Couples

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Previous studies have reported that related human couples tend to produce more children than unrelated couples but have been unable to determine whether this difference is biological or stems from socioeconomic variables. Our results, drawn from all known couples of the Icelandic population born between 1800 and 1965, show a significant positive association between kinship and fertility, with the greatest reproductive success observed for couples related at the level of third and fourth cousins. Owing to the relative socioeconomic homogeneity of Icelanders, and the observation of highly significant differences in the fertility of couples separated by very fine intervals of kinship, we conclude that this association is likely to have a biological basis.

There has been long-standing uncertainty about the impact of kinship or consanguinity between spouses on the total number of offspring they produce (completed fertility). Consanguineous unions among humans increase the probability of a zygote receiving the same deleterious recessive alleles from both parents, with a possible adverse effect on fertility through an increased rate of miscarriage, infant mortality, and morbidity (*1*–*3*). Conversely, consanguineous unions may confer greater completed fertility through earlier age at marriage, as well as the socioeconomic advantages associated with preserving land and wealth within extended families. (*4*, *5*). In other species, lower fitness has been observed in offspring of distantly related individuals, which appears to be a result of the breakdown of coadapted gene complexes (*6*).

Previous studies examining the relationship between kinship and fertility in humans have focused on relatively close relationships between couples, rarely evaluating relationships more distant than second cousins (who share two great-grandparents) (*4*). Such studies have tended to be

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Table 1. A summary of kinship and fertility in 25-year intervals from 1800 to 1965. Shown are descriptive statistics for kinship coefficients and three variables that reflect the completed fertility (the total number of offspring) and reproductive success (the total number of children who reproduce and the total number of grandchildren) of the couples.

	All couples					Couples with $q_\Phi > 0$	
Birth year of female	*N*	Mean q_Φ (SE)*	Mean number of offspring per couple (SE)	Mean number of offspring that reproduce per couple (SE)	Mean number of grandchildren per couple (SE)	*N*	Mean kinship $\Phi \times$ 1000 (25–75 percentiles)
1800–1824	8,673	0.426 (0.0021)	3.610 (0.0359)	1.765 (0.0195)	7.901 (0.1051)	8,362	4.93 (0.004–1.012)
1825–1849	14,338	0.514 (0.0013)	3.468 (0.0254)	1.639 (0.0146)	7.384 (0.0768)	14,109	5.45 (0.029–1.195)
1850–1874	15,863	0.606 (0.0011)	3.221 (0.0234)	1.749 (0.0157)	7.193 (0.0733)	15,575	4.76 (0.054–1.257)
1875–1899	16,691	0.672 (0.0012)	3.392 (0.0231)	2.430 (0.0180)	9.053 (0.0758)	16,268	3.70 (0.043–1.050)
1900–1924	24,732	0.721 (0.0011)	2.791 (0.0143)	2.360 (0.0127)	7.467 (0.0450)	23,799	2.01 (0.024–0.562)
1925–1949	39,635	0.759 (0.0010)	2.547 (0.0087)	1.996 (0.0083)	4.983 (0.0237)	37,762	0.82 (0.022–0.336)
1950–1965	40,879	0.782 (0.0012)	2.004 (0.0058)	0.501 (0.0038)	0.864 (0.0075)	38,336	0.50 (0.033–0.306)
Total	160,811	0.695 (0.0005)	2.740 (0.0058)	1.648 (0.0046)	5.330 (0.0182)	154,211	2.22 (0.029–0.526)

*q_Φ is a weighted measure of the genealogical information available to calculate the kinship of couples, with values between 0 (when at least one spouse has no known ancestor) and 1 (when all ancestors are known for both spouses). See (*10*) for more details.

performed in populations with relatively high rates of consanguineous marriages, such as those of India, Pakistan, and the Middle East (*4*, *7*–*9*); however, these populations also tend to be characterized by large socioeconomic disparities.

To explore the relationship between fertility and kinship in humans, we examined 160,811 Icelandic couples from the deCODE Genetics genealogical database born between 1800 and 1965 (*10*). The advantage of using the Icelandic data set lies in this population being small and one of the most socioeconomically and culturally homogeneous societies in the world (*11*), with little variation in family size, use of contraceptives, and marriage practices (*12*), in contrast with most previously studied populations (*4*, *7*–*9*). By estimating kinship based on a depth of up to 10 generations from each couple, we were able to assess differences in fertility across a fine scale of kinship values. Our data indicated that there has been a decrease by a factor of 10 in mean kinship between Icelandic couples during the past two centuries, from 0.005 for couples with females born 1800 to 1824 to 0.0005 for those born 1950 to 1965 (Table 1). This is equivalent to a change from couples being related on average between the level of third and fourth cousins to couples being related on average at the level of fifth cousins. The primary cause is probably a demographic transition from a poor agricultural society to an affluent industrial society, involving extensive migration from rural regions to urban centers, accompanied by a rapid expansion in population size (*13*). The outcome of this transition is an expansion of the pool of potential mates for contemporary Icelanders, particularly those who are distantly related. Typically, this kind of demographic transition results in a drop in the average number of children per couple with time (Table 1). However, this relationship is not monotonic for the Icelandic data (fig. S1). To compare the kinship and fertility of couples born between 1800 and 1965, we standardized the variables documenting kinship, the number of children per couple, and other measures of reproductive success (*10*).

A monotonic positive relationship was observed between the degree of kinship among spouses and the number of children they produced (Fig. 1A). Furthermore, the reproductive success of the couples, as reflected by the number of their children who reproduced (Fig. 1B), followed an n-shaped curve from the relatively low reproductive success of couples related at the level of second cousins or closer, to the maximum for couples related at the level of third and fourth cousins, after which there is a steady decrease in reproductive success with diminishing kinship between spouses. A similar picture emerges when the number of grandchildren per couple is examined (Fig. 1C).

These results are based on couples born during a period of almost 200 years, in the course of which there was a marked decline both in the mean fertility and in kinship between couples (Table 1). Nonetheless, the same general relationship between kinship and reproductive outcome was observed within each 25-year subinterval (fig. S2). We evaluated the correlation between the standardized variables of kinship and reproductive outcome for all couples and for each time interval separately (Table 2), adjusting for the impact of geographical differences in the kinship and fertility of couples within Iceland (*10*). Each test revealed a significant association with kinship, with correlation coefficients of 0.063 ($P = 1.5 \times 10^{-129}$) for the number of children, 0.045 ($P = 3.6 \times 10^{-66}$) for the number of children who reproduced, and 0.042 ($P = 7.6 \times 10^{-58}$) for the number of grandchildren. To assess the potential impact of q_Φ (the amount of information available to calculate the kinship coefficient, Φ, for each couple) on the key variables of kinship and reproductive outcome, we also performed the correlation analyses for the subset of 112,683 couples for whom all ancestors are known four generations back in time (Table 2). Almost identical results were obtained for couples born after 1850. For couples born before 1850, the association with fertility was statistically significant, but not with the two indicators of reproductive success (i.e., children and grandchildren), primarily because so many couples with incompletely known ancestral genealogies had to be omitted from the analysis.

Although the general pattern is one of both greater fertility and reproductive success with increasing kinship between spouses, there was a notable deficit in the reproductive success of couples related at the level of second cousins or closer (Fig. 1, B and C). Figure 1D shows that this deficit was partly accounted for by a shorter average life span of children produced by such couples (see also fig. S3). However, because there was still a strong monotonic relationship between kinship and fertility of couples when we restricted analysis to the number of children who survived to the age of 30 years, the lower reproductive success of the most related couples may also stem from greater morbidity or mortality of their offspring during adulthood (fig. S4). We do not find evidence for a sex difference in such reproductive costs among offspring (fig. S5).

Although Icelanders have experienced a socioeconomic transformation from 1800 to the present (*14*, *15*), accompanied by a reduction in family size and decreasing kinship between couples (Table 1), essentially the same relationship between kinship and fertility was observed at the beginning and end of this 200-year period (fig. S2). By estimating kinship between spouses at a genealogical depth of up to 10 generations, it was possible to examine the association with fertility and reproductive success at a very fine scale. Thus, for example, there is a statistically significant difference in the number of children produced by couples related at the level of sixth versus seventh cousins ($P = 1.4 \times 10^{-7}$). Relationships at this genealogical distance are rarely known to the couples or their families and acquaintances in their social environment and are unlikely to influence factors such as age at the commencement of reproduction or the practice of consanguineous unions to preserve family property (*4*, *16*).

Although some interaction of fertility and kinship with socioeconomic factors cannot be

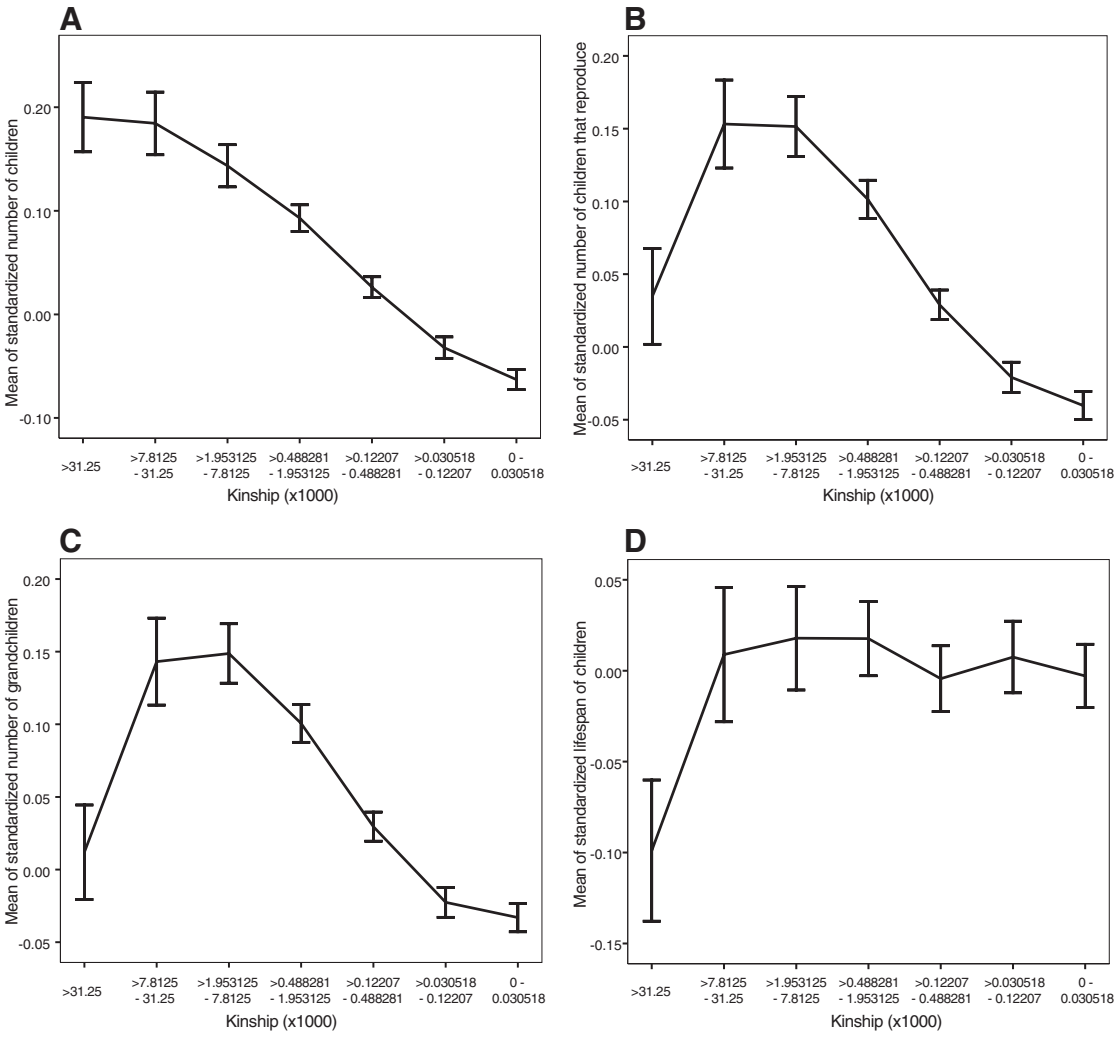

Fig. 1. The relationship between kinship and reproduction among Icelandic couples. The four panels show means and 95% confidence intervals of standardized variables relating to the reproductive outcome of Icelandic couples as a function of seven intervals of kinship. (**A**) shows the total number of children, (**B**) the number of children who reproduced, (**C**) the number of grandchildren, and (**D**) the mean life expectancy of children. The first interval of kinship represents all couples related at the level of second cousins or closer, the second interval represents couples related at the level of third cousins and up to the level of second cousins, and so on, with each subsequent category representing steps to fourth, fifth, sixth, and seventh cousins and the final category representing couples with no known relationship and those with relationships up to the level of eighth cousins.

Table 2. The correlation between kinship and reproductive outcome.

	All couples				Couples with all ancestors known four generations back			
Birth year of female	*N*	Number of children Pearson's *r* (*P* value)	Children who reproduce Pearson's *r* (*P* value)	Grandchildren Pearson's *r* (*P* value)	*N*	Number of children Pearson's *r* (*P* value)	Children who reproduce Pearson's *r* (*P* value)	Grandchildren Pearson's *r* (*P* value)
1800–1824	8,346	0.071 (4.7×10^{-10})	0.054 (1.6×10^{-6})	0.057 (3.8×10^{-7})	1,401	0.130 (5.1×10^{-3})	0.022 (6.2×10^{-1})	0.022 (6.3×10^{-1})
1825–1849	14,050	0.085 (8.8×10^{-23})	0.042 (1.5×10^{-6})	0.037 (1.8×10^{-5})	4,783	0.088 (1.4×10^{-5})	0.027 (1.7×10^{-1})	0.013 (5.2×10^{-1})
1850–1874	15,440	0.088 (2.2×10^{-26})	0.053 (1.2×10^{-10})	0.045 (5.4×10^{-8})	10,568	0.097 (2.4×10^{-18})	0.046 (3.1×10^{-5})	0.037 (7.9×10^{-4})
1875–1899	16,150	0.080 (7.2×10^{-23})	0.053 (4.4×10^{-11})	0.047 (7.0×10^{-9})	13,563	0.080 (3.4×10^{-18})	0.049 (8.4×10^{-8})	0.042 (3.5×10^{-6})
1900–1924	23,740	0.072 (2.3×10^{-27})	0.067 (4.9×10^{-24})	0.065 (6.0×10^{-23})	21,022	0.076 (1.5×10^{-25})	0.068 (6.0×10^{-21})	0.067 (2.1×10^{-20})
1925–1949	36,733	0.056 (4.0×10^{-27})	0.049 (4.1×10^{-21})	0.047 (2.1×10^{-19})	31,510	0.059 (2.8×10^{-23})	0.051 (4.4×10^{-18})	0.05 (1.1×10^{-17})
1950–1965	36,510	0.034 (6.4×10^{-11})	0.020 (1.5×10^{-4})	0.018 (6.5×10^{-4})	29,836	0.034 (1.6×10^{-8})	0.027 (2.3×10^{-5})	0.025 (9.8×10^{-5})
All	150,969	0.063 (1.5×10^{-129})	0.045 (3.6×10^{-66})	0.042 (7.6×10^{-58})	112,683	0.063 (2.1×10^{-86})	0.046 (2.8×10^{-46})	0.043 (6.1×10^{-41})

ruled out, our results support the hypothesis that the positive association between kinship and fertility has a basis in reproductive biology. A positive relationship between kinship and reproductive success seems counterintuitive from an evolutionary perspective. We did find some evidence of a reproductive cost borne by offspring of parents related at the degree of second cousins or closer. Strikingly, however, our results show that couples related at the degree of third to fourth cousins exhibited the greatest reproductive success.

The formation of densely populated urban regions that offer a large selection of distantly related potential spouses is a new situation for humans in evolutionary terms. We note that if the relationship between kinship and fertility has a basis in human reproductive biology, then it follows that the kind of demographic transition recently experienced by the Icelandic population could directly contribute to the slowing of population growth elsewhere through the relative increase of distantly related couples.

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Mutations in the Pericentrin (*PCNT*) Gene Cause Primordial Dwarfism

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Fundamental processes influencing human growth can be revealed by studying extreme short stature. Using genetic linkage analysis, we find that biallelic loss-of-function mutations in the centrosomal pericentrin (*PCNT*) gene on chromosome 21q22.3 cause microcephalic osteodysplastic primordial dwarfism type II (MOPD II) in 25 patients. Adults with this rare inherited condition have an average height of 100 centimeters and a brain size comparable to that of a 3-month-old baby, but are of near-normal intelligence. Absence of PCNT results in disorganized mitotic spindles and missegregation of chromosomes. Mutations in related genes are known to cause primary microcephaly (*MCPH1*, *CDK5RAP2*, *ASPM*, and *CENPJ*).

The growth of an individual depends on regulation of cell size and cell division. Dysfunction of these regulatory pathways not only results in somatic undergrowth but contributes to a wide variety of pathological conditions, including cancer and diabetes (*1*). To identify potential regulators of human growth, we used positional cloning to determine the underlying defect in a rare autosomal recessive disorder characterized by extreme pre- and postnatal growth retardation, namely, microcephalic osteodysplastic primordial dwarfism type Majewski II [MOPD II, Mendelian Inheritance in Man (MIM) 210720].

Individuals with MOPD II have an average birth weight of less than 1500 g at term, an adult height of about 100 cm, and a variety of associated bone and dental anomalies (Fig. 1) (*2*, *3*). Despite the small head size (average postpubertal head circumference of 40 cm), brain development appears grossly normal with only a few individuals displaying serious mental retardation, a feature that sets MOPD II apart from primary microcephaly and Seckel syndrome. Far-sightedness, irregular pigmentation, truncal obesity, and type 2 diabetes with onset at or before puberty have been noted in older individuals with MOPD II, and life expectancy is reduced because of a high risk of stroke secondary to cerebral vascular anomalies, often classified as Moyamoya disease (*2*, *4*). Although these features led investigators to hypothesize that MOPD II is a premature aging syndrome (*5*), we found no evidence of accelerated telomeric shortening as a potential cellular explanation of premature aging in lymphocyte samples of two unrelated female patients with MOPD II (P1 and P2) (fig. S1) (*6*). MOPD II patients do not show an enhanced predisposition to cancer; consistent with this, patient lymphocytes did not show an increased frequency of sister chromatid exchange (table S1), as would be indicative of a defect in DNA repair, and typical of another syndrome associated with significant short stature, namely, Bloom syndrome (MIM 210900).

Consanguinity in the respective parents of the two unrelated female patients P1 and P2 presented the possibility of locating a MOPD II locus by homozygosity mapping (*6*, *7*) (Fig. 2A). This approach allows the identification of an autosomal recessive disease locus by tracking its segregation within a common chromosomal segment that originates from a shared recent ancestor and is transmitted through both parents. Genome-wide linkage analysis using polymorphic short tandem repeat markers revealed a single disease locus on chromosome 21q22.3. When a third consanguineous family was included, a maximum lod (logarithm of the odds ratio for linkage) score of 3.7 was obtained at marker *D21S1446* (Fig. 2 and fig. S2), confirming linkage to this locus. The linked region encompasses 4.6 megabases at the distal end of chromosome 21 and contains the pericentrin (*PCNT*) gene, which we considered a suitable candidate gene because of its postulated role in chromosome segregation. Mutational analysis of the 47 exons of *PCNT* in 25 unrelated patients with a clinical diagnosis of MOPD II, including those from the three linked families, revealed homozygous and compound heterozygous

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An Association Between the Kinship and Fertility of Human Couples

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