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Mutations in the pre-replication complex cause Meier-Gorlin syndrome

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Meier-Gorlin syndrome (ear, patella and short-stature syndrome) is an autosomal recessive primordial dwarfism syndrome characterized by absent or hypoplastic patellae and markedly small ears[1–3]. Both pre- and post-natal growth are impaired in this disorder, and although microcephaly is often evident, intellect is usually normal in this syndrome. We report here that individuals with this disorder show marked locus heterogeneity, and we identify mutations in five separate genes: *ORC1*, *ORC4*, *ORC6*, *CDT1* and *CDC6*. All of these genes encode components of the pre-replication complex, implicating defects in replication licensing as the cause of a genetic syndrome with distinct developmental abnormalities.

hypothesize that further pre-replication complex genes might cause primordial dwarfism; however, we did not find mutations in other ORC subunits.

In this study, the profound growth retardation and microcephaly in an individual with a complex lethal developmental syndrome led us to screen him for *ORC1* mutations. We found that this individual and his brother (called here P1 and P2; **Table 1** and **Supplementary Table 1**) were compound heterozygote for mutations in *ORC1* (p.Arg105Gln and p.Val667*fs*X24). The combination of truncating and missense mutations present in these individuals was in contrast to biallelic missense mutations seen in previous *ORC1* cases, suggestive of greater loss-of-function and consistent with a more severe phenotype. Unlike previous *ORC1* cases, the proband (P1) had an extensive number