Single gene defect found for unexplained dwarfism

Mutations in a DNA replication gene cause a rare developmental disorder seen in Saudi children.

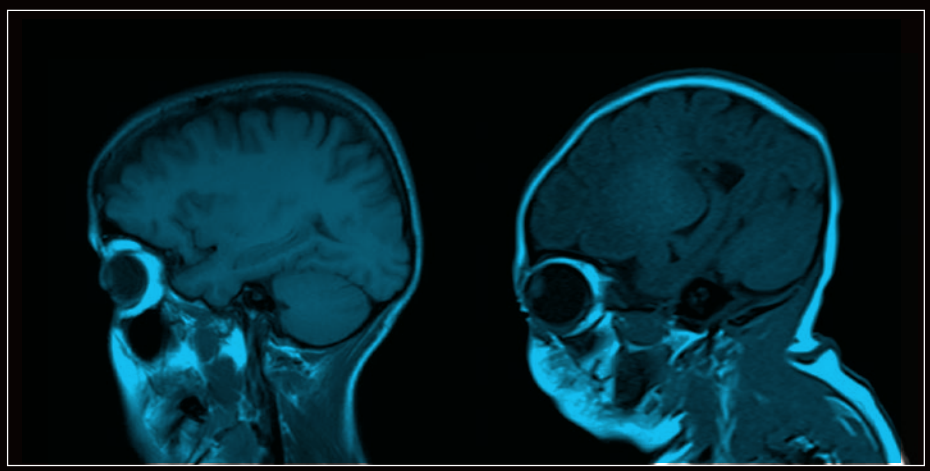
A study co-led by researchers in Saudi Arabia and the United Kingdom has identified the faulty gene behind a developmental disorder that often causes shrunken heads and short stature in Saudis.

Before this discovery, the study participants, from across Europe, North America, Africa and the Middle East, had no idea what was causing their family's disease and clinicians had no way of preventing more children being born with this debilitating illness, known as microcephalic dwarfism. Now they can point to defects in a gene called DONSON, which is needed for DNA to be faithfully copied when cells divide and grow.

"We're pleased that these families were finally able to have molecular diagnosis enabled by this discovery, so they can avoid recurrence," says Fowzan Alkuraya, a clinical geneticist at the King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh and a lead investigator of the study.

One of the participating families was evaluated at Riyadh's King Abdulaziz Medical City (KAMC) by a team that included Mohammed Al Balwi, a molecular geneticist at KAIMRC and a co-author of the study. Both KAMC and KFSHRC, in addition to several other Saudi hospitals, now have prenatal screening programmes designed to target DONSON mutations in prospective parents so they can avoid passing the gene on to offspring.

Alkuraya and his colleagues pinpointed the gene by sequencing the protein-coding DNA of children with unexplained microcephalic dwarfism. In total, they found 29 affected individuals from 21 families who all had a small head and reduced height, and who all carried mutations in both copies of the DONSON gene. Eight of the families were from Saudi Arabia, where marriage between cousins is common and leads to a high rate of birth disorders.



Brain scans from children with normal (left) and mutated (right) versions of the DONSON gene.

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Collaborators in the United Kingdom then characterized the consequence of these mutations on a cellular level. For some patients, the mutations altered the coding sequence of the protein produced by DONSON. But for all of the patients from Saudi Arabia, the mutations fell in a non-coding region that altered how the genetic code got processed, leading to an aberrant and less abundant protein product.

Either way, the loss of a functional DONSON gene impaired the body's ability to copy DNA fast enough to keep pace with the needs of the early growing brain and body, explaining how a single mutation could have such a devastating effect.

Reynolds, J. J., Bicknell, L. S., Carroll, P., Higgs, M.R., Shaheen, R. *et al.* Mutations in *DONSON* disrupt replication fork stability and cause microcephalic dwarfism. *Nature Genetics* **49**, 537–549 (2017).