

PTPN analysis was done in 79 individuals; mutations were found in 35%. The mutations were more likely to be found in familial cases (50%).

Height SDS at entry into the study was -2.184 and at follow-up was -1.755 . Twelve individuals received growth hormone (GH) treatment. There were no statistical differences in the height SDS between those who received and those who had not received GH therapy. Those with *PTPN* mutations had similar mean height SDS. Final adult height was 167.4 cm (males) and 152.7 cm (females). When the individuals who received GH treatment were excluded, the mean final height increased to 169.8 cm (males) and 153.3 cm (females) as those who received GH were shorter. The final height in those with the *PTPN11* mutation was about 4 cm less than the others. Pulmonary stenosis was present in 65% and more prevalent in those with the mutation. No intervention was required in 58% of subjects. Hypertrophic cardiomyopathy was present in 19%; 9 of these subjects also had pulmonary stenosis. Five individuals died from complications related to hypertrophic cardiomyopathy and one person had a cardiac transplant. Feeding difficulties at ascertainment were common; some were associated with developmental speech delay. Approximately 73% of these individuals attended mainstream schools while 27% attended schools for children with learning disabilities (the mutation was equally distributed between the 2 groups); 16% had achieved higher education (this compares with 25% of the UK population). Sixty percent were full-time employed, while 26% were registered as disabled. Orthodontic work had been performed on 51%. Six percent of the individuals had required hormone injections to induce puberty. Puberty was somewhat delayed, starting at 14.5 years (males) and 14 years (females). Of those individuals who attempted to have children, 67% experienced no problems. Easy bruising or bleeding was seen in about 79%, but not associated with any known coagulopathy; prevalence of the *PTPN* mutation was higher in those with a history of easy bruising. Refractive errors were seen in 71% of the individuals. Lymphedema affected the lower limbs of 2, and scoliosis was present in 13%. Approximately 13% had recurrent seizures; *PTPN11* mutations were identified in 2 of those. All subjects, with the exception of 4, had normal hearing at follow-up.

The authors stated that their longitudinal follow-up was one of the largest databases on well-characterized Noonan syndrome. However, they have some potential bias in follow-up data because of the individuals who had dropped out. They also pointed out that they could not correlate the *PTPN* mutations with short stature as others have demonstrated. They found that about 10% of the subjects with mutations had hypertrophic cardiomyopathy.

Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. *Arch Dis Child.* 2007;92:128-32.

Editor's Comment: *Shaw and colleagues are to be congratulated in following a large group of individuals with Noonan syndrome from childhood through adulthood and final height. Their data do not confirm the data of others with regard to mutations and short stature. Studies from France, Brazil, and Germany have demonstrated different findings with regard to Noonan syndrome. Limal et al¹ showed that individuals with the PTPN11 mutation have poor growth and do not respond to GH administration as well as those without the mutation. Ferreira et al² have also shown reduced GH response to long-term GH treatment. Finally, Binder et al³ have shown that those with SHP-2 mutation have mild GH resistance and also poor GH response. Thus it is not surprising that the individuals treated with GH in the current longitudinal study, although shorter, also ended up shorter than those who had not been treated. Other studies will be needed in order to determine whether higher doses of GH or insulin like growth-factor (IGF)-I treatment⁴ may enhance final height of those children with Noonan syndrome who have the PTPN11 mutation.*

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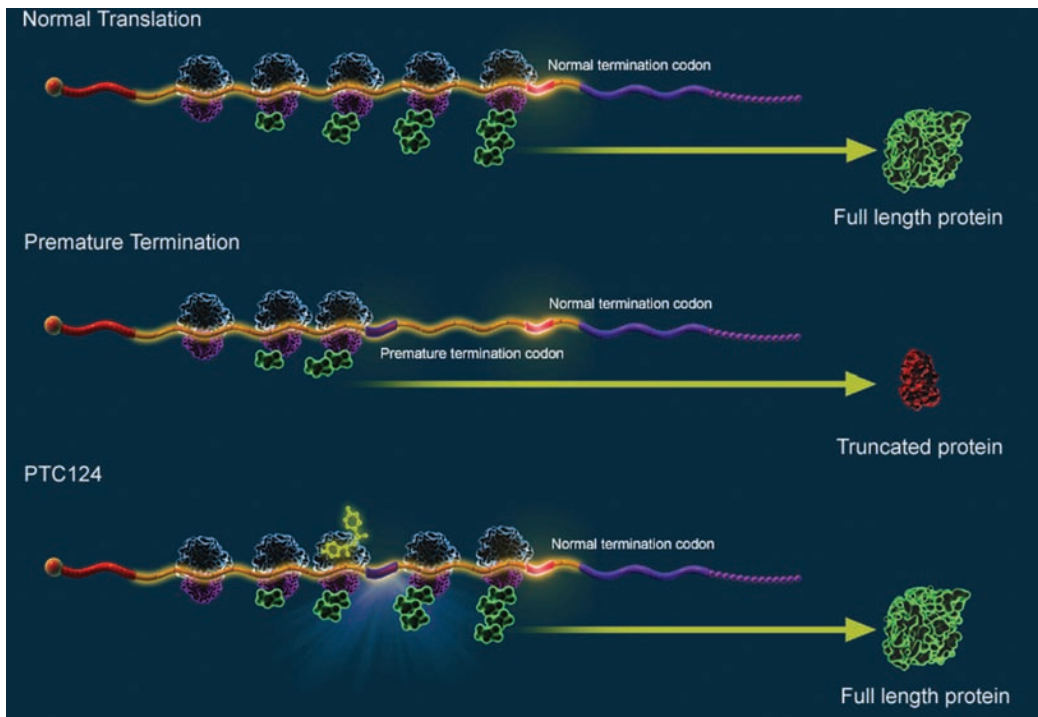
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1. Limal JM, Parfait B, Cabrol S, et al. *J Clin Endocrinol Metab.* 2006;91:300-6.
2. Ferreira LV, Souza SA, Arnhold IJ, et al. *J Clin Endocrinol Metab.* 2005;90:5156-60.
3. Binder G, Neuer K, Ranke MB, et al. *J Clin Endocrinol Metab.* 2005;90:5377-81.
4. Kim RJ, Grimberg A. *Growth Genet Horm.* 2007;23:1-7.

Nonsense Mutations in Genetic Disease—A Novel Treatment

Nonsense mutations are a common cause of human genetic disease. They give rise to in-frame premature translation termination or stop codons within the coding regions of genes and lead to truncated protein translation products that are typically nonfunctional and also promote mRNA destruction by so-called nonsense-mediated mRNA decay (NMD). The idea of developing pharmacologic means to induce a cell's translation machinery to readthrough premature termination

codons (PTCs) has been around for some time, and there is evidence that the antibiotic gentamicin prompts ribosomes to readthrough PTCs to generate full-length proteins (Figure). In fact, gentamicin has received attention in this context and preliminary trials have been carried out in patients with Duchenne muscular dystrophy (DMD) and cystic fibrosis due to mutations that introduce PTCs. However, the high doses that are required, potential for renal and otic toxicity and



Translation of an mRNA into protein: comparison of normal translation, premature translation termination, and treatment with PTC124 restoring synthesis of full-length protein. Reprinted with permission from PTC Therapeutics.

need for intravenous or intramuscular administration of gentamicin have limited its potential usefulness for treatment of human diseases. A new compound has now been identified that appears to suppress PTCs with fewer potential problems.

Welch et al utilized high-throughput screening of ~800,000 compounds to identify small molecules that would suppress PTCs. One compound designated PTC124 promoted dose-dependent readthrough of PTCs, including human and mouse nonsense alleles of the dystrophin gene. Compared to gentamicin, PTC124 was effective at much lower doses and it could be delivered orally. After documenting an increase in dystrophin protein levels in primary muscle cell cultures, they then treated *mdx* mice, a mouse model of DMD due to a mutation-induced PTC in the dystrophin gene.

PTC124 treatment led to partial rescue of the muscle disturbance in the *mdx* mice. The most notable functional result was protection against susceptibility to contraction-induced injury. This injury, which is a typical feature of the *mdx* mouse and most likely occurs in DMD patients, involves repeated cycles of degeneration—regeneration, inflammation, and necrosis that eventually leads to muscle destruction. Susceptibility to this injury for mice treated with PTC124 was no different than for wild-type mice.

Mdx mice treated with PTC124 for 8 weeks showed significant decreases in serum creatinine kinase levels compared to untreated controls. Their muscle tissues displayed increased levels of dystrophin protein as well as γ -sarcoglycan consistent with production and stabilization of the dystrophin-associated membrane complex

that is missing in the absence of dystrophin. Drug treatment also led to a partial restoration of dystrophin to the membrane of skeletal muscles, although the relative amount appeared to be less than in wild type mice.

The authors concluded that PTC124 is a more potent nonsense mutation suppressing agent than gentamicin. They attribute its effect to directly suppressing premature termination during translation rather than to interference with NMD. Importantly, they also provided evidence that it does not affect the function of normal

termination codons. The authors suggested that through increasing the efficiency of translation, PTC124 may benefit patients with genetic diseases due to nonsense mutations. An accompanying news and views comment indicated that Phase II clinical trials are underway for PTC124 in DMD and cystic fibrosis.

Welch EM, Barton ER, Zhuo J, et al. PTC124 targets genetic disorders caused by nonsense mutations. *Nature*. 2007;447:87-93.

Schmitz A, Famulok M. Chemical biology: ignore the nonsense. *Nature*. 2007;447:42-3.

Editor's Comment: *The research described in this paper could have significant impact on the treatment of a subset of genetic disease. It reflects a marriage between so called chemical biology, which seeks to identify small molecules that produce desired therapeutic effects on disease processes, and continued efforts to understand the molecular consequences of mutations. It underscores an importance of DNA diagnoses.*

The paper raises the concern that suppressing PTCs would lead to synthesis of mutant proteins. In many instances such as enzymopathies and disorders in which structural proteins serve as platforms for or link together cellular machinery, such as in DMD, having more protein even if it harbors a mutation, would seem beneficial. However, there may also be instances where having no protein is better for a cell or a tissue than having a mutant protein that adversely affects other normal molecules.

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