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Phenotypic Reversion of Fair Hair upon Gene Therapy of the Phenylketonuria Mice

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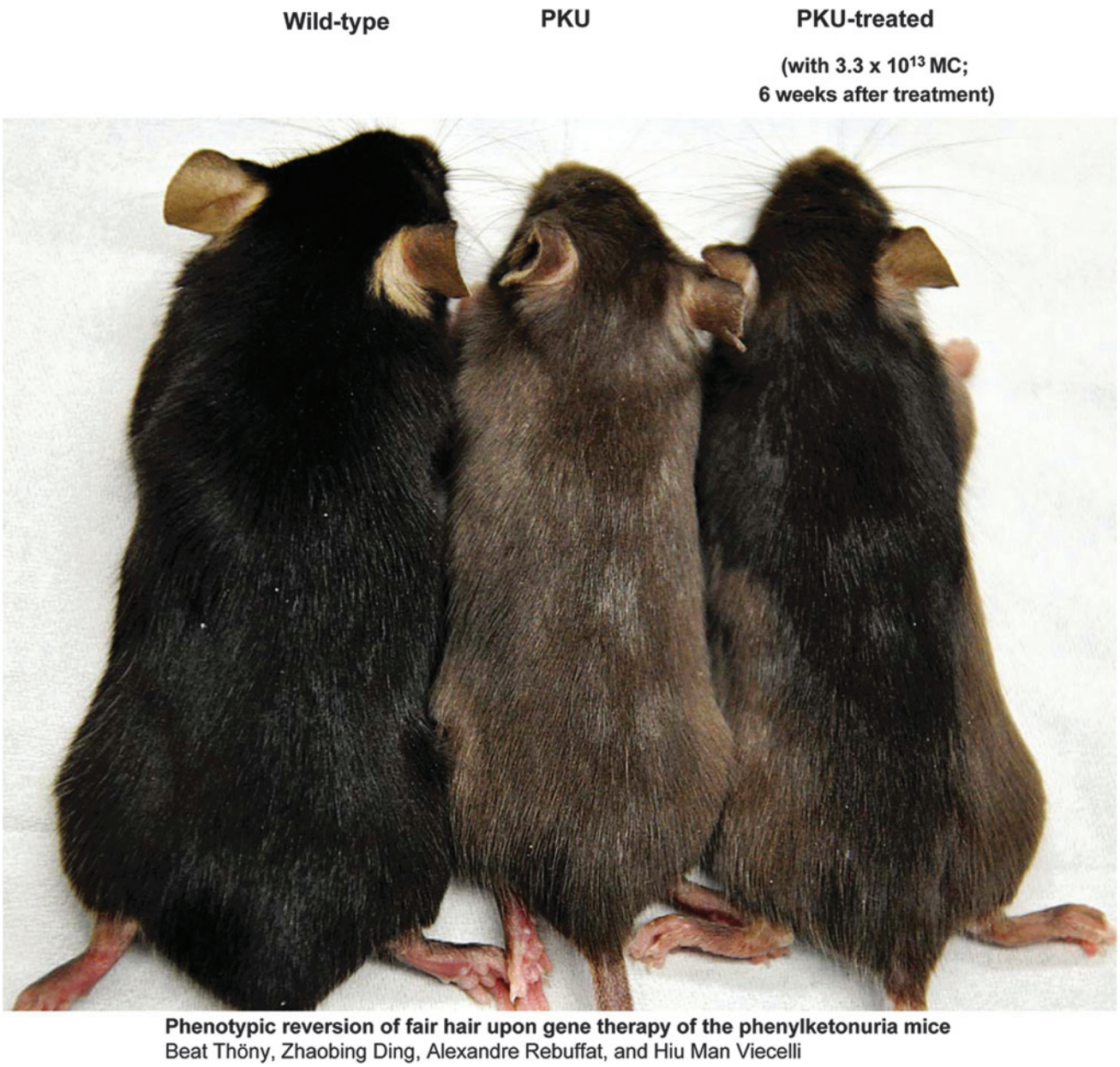

FIG. 1. Phenotypic reversion from brown to black coat color of treated phenylketonuria (PKU) (*Pah-enu2*) mouse (see text for details).

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PHENYLKETONURIA (PKU) (OMIM261600) is an autosomal recessive genetic disorder characterized by accumulation of the essential amino acid L-phenylalanine (L-Phe) in the body caused by deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH; EC 1.14.16.1). Owing to attenuated biosynthesis of melanin due to systemic elevated L-Phe, hypopigmentation is one of the visible phenotypes of PKU. Such a phenotype can also be observed in PKU mice bearing the homozygous *Pah-enu2* allele, where it was reported that restoration of hypopigmentation needs at least 5% of the PAH enzyme activity (Fang *et al*., 1994; Nagasaki *et al*., 1999; Viecelli *et al*., 2014). This phenotype was reversed in black 6 (C57Bl/6) PKU mice to wild-type level after hydrodynamic tail vein injection of a recombinant nonviral minicircle-based naked DNA vector expressing the murine *Pah*-cDNA from a liver-specific promoter. Young adult C57Bl/6 untreated wild-type and PKU mice carrying homozygously the *Pah-enu2* allele are shown in Figure 1 before (middle), and 6 weeks after infusion of the minicircle vector MC.PKU20 (Viecelli *et al.*, 2014). Fair-haired PKU mice started to darken after gene transfer and eventually became indistinguishable from wild-type. Changes from brown to black hair persisted from then on in minicircle vector–treated mice. Normalization of blood L-Phe concomitant with reversion of hypopigmentation in a dose-dependent manner can also be observed with other gene therapeutic vectors such as, for instance, after treatment of PKU with AAV2 serotype 8 (rAAV2/8-PKU5) to target liver or with rAAV2/1-mediated intramuscular expression of a complete L-Phe hydroxylating system (Ding *et al*., 2006, 2008).

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