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Evaluation of risk modification for *p*-phenylenediamine sensitization by *N*-acetyltransferase 1 and 2 for two highly sensitive cases

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p-Phenylenediamine (PPD) (1,4-diaminobenzene; CAS no. 106-50-3) is well known as key allergen in hair dye-related allergic contact dermatitis. PPD can be *N*-acetylated to the non-sensitizing compounds mono-PPD (MAPPD) and diacetyl-PPD (DAPPD) by *N*-acetyltransferase 1 (NAT1) in keratinocytes,¹ and outside the skin also by *N*-acetyltransferase 2 (NAT2).² When investigating the elicitation response modification by NAT1 and NAT2 genotypes, we showed that genotypes containing the rapid acetylator allele NAT1*10 and individuals homozygous for the rapid acetylator allele NAT2*4 were under-represented among PPD-sensitized cases.³ Here, we evaluated this finding by investigating two well-characterized highly sensitive cases with a longstanding history of allergic contact dermatitis caused by dyes.

CASE REPORTS

Case 1 was a 41-year-old woman who had been dyeing her hair and eyelashes with permanent black hair dye 6 to 10 times a year for

5 years. She developed itching, erythema, vesicles, infiltration and oedema of her scalp, forehead, neck and ears after dyeing her eyelashes with permanent black hair dye.

Case 2 was a 19-year-old female trainee hairdresser who had been dyeing her hair >10 times a year for approximately 4 to 6 years. She showed erythema and pruritus of her hands and scalp after working with hair dyes and dyeing her own hair and eyelashes with semi-permanent and permanent hair dyes, respectively. Furthermore, an eczematous skin reaction to a black henna tattoo in the past was recalled.

Both individuals had positive patch test reactions to PPD 90 µg/cm² (TRUE Test; SmartPractice Europe, Reinbek, Germany). Patch testing was performed with 20 mg of MAPPD 1% pet. and 20 mg of DAPDD 1% pet. (purity of >98.0% by high-performance liquid chromatography; supplied by Procter & Gamble, Mason, Ohio). Van der Bend Chambers were used (Van der Bend, Brielle, The Netherlands), fixed with Fixomull Stretch (BSN Medical, Hamburg,

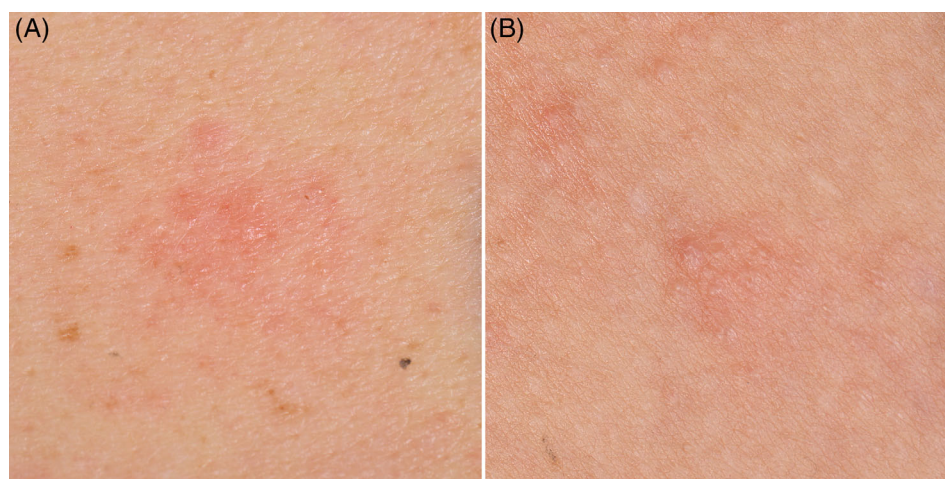


FIGURE 1 (A), Case 1, positive patch test reaction (+) to mono-*p*-phenylenediamine 1% pet. on day 3. (B), Case 2, positive patch test reaction (+) to diacetyl-*p*-phenylenediamine 1% pet. on day 3

TABLE 1 Positive patch test reactions in the routine diagnostic workup at first consultation and during study follow-up

Case 1				Case 2			
Positive test results May 2002: Routine diagnostic work-up first consultation				Positive test results March 2014: Routine diagnostic work-up first consultation			
	D2	D3		D3	D7		
Nickel sulfate 200 µg/cm ²	+	+		PPD (free base) 90 µg/cm ²	++	+	
PPD (free base) 90 µg/cm ²	+	+++		Toluene-2,5-diamine 1.0%	++	+	
Disperse Orange 3 1.0% pet.	++	+++					
4,4-Diaminodiphenylmethane 0.5% pet.	–	+					
4-Aminoazobenzene 0.25% pet.	+	+++					
Toluene-2,5-diamine 1.0%	–	++					
Positive test results December 2015	D2	D3	D7	Positive test results January 2016	D2	D3	D7
Open use test PPD 2%	+++	+++	+++	Open use test PPD 2%	+++	+++	+++
Open use test ME-PPD 2%	++	++	++	Open use test ME-PPD 2%	+	+	+
ME-PPD 0.5%	+++	+++	+++	ME-PPD 0.5%	++	++	+
ME-PPD 1%	+++	+++	++	ME-PPD 1%	++	++	+
ME-PPD 2%	+++	+++	++	ME-PPD 2%	++	+++	+
MAPPD 1% pet.	?+	+	–	MAPPD 1%	?+	?+	–
DAPPD 1% pet.	–	–	–	DAPPD 1%	+	+	–

Abbreviations: DAPPD, diacetyl-*p*-phenylenediamine; MAPPD, mono-*p*-phenylenediamine; ME-PPD, 2-methoxymethyl-*p*-phenylenediamine; PPD, *p*-phenylenediamine.

Germany). The patch tests were applied on the back for 48 hours under occlusion, and patch test readings were performed on day (D) 2, D3, and D7, according to ESCD guidelines. Case 1 showed a doubtful reaction to MAPPD 1% on D2, and a + positive patch test reaction to MAPPD 1% on D3. Case 2 showed doubtful reactions to MAPPD 1% on D2 and D3, and + positive reactions to DAPPD 1% on D2 and D3 (Figure 1).

Both patients were included in a previous study of 25 PPD-allergic subjects in whom cross-elicitation responses to 2-methoxymethyl-*p*-phenylenediamine were evaluated and compared with reactions to PPD in open use testing and diagnostic patch testing.⁴ Of all 25 patch tested patients, only the two cases that we describe in this report showed positive reactions to MAPPD and DAPPD. Table 1 shows the results of patch testing and open use testing.

We studied the acetylation status of both cases, and analysed all known variant loci, including rare single-nucleotide polymorphisms, by using a DNA sequencing-based method and statistical haplotype reconstruction. For NAT1, we observed that both cases were homozygous for the NAT1 reference allele NAT1*4/*4 and for NAT2, we found NAT2*4/*5B for case 1 and NAT2*5B/*7A for case 2. These results give no indication for a fast acetylase phenotype. Thus, despite the limited capacity of N-acetylated PPD to reactivate T cells from allergic patients *in vitro*⁵ and *in vivo*,⁶ we confirmed our earlier results and found very sensitive individuals who also reacted to MAPPD (case 1) and MAPPD and DAPPD (case 2).

In line with our previous results, which showed rapid acetylators to be under-represented among PPD-allergic cases,³ we found only reference-type acetylators for NAT1 or slow and intermediate NAT2 acetylators among the cases.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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