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Editor,

Androgenetic alopecia (AGA) is the most common form of hair loss in humans. Evidence suggests the participation of prostaglandins in the development of AGA. The aim of this study was to analyze the expression of the *PTGDR2* (GPR44 receptor), *PTGDS* (Prostaglandin D2 synthase), and *PTGES* (Prostaglandin E synthase) transcripts in biopsies from balding scalp of hispanic patients with AGA and female androgenetic alopecia (FAGA).

Thirty-two hispanic patients were included: 16 patients with clinically and dermatoscopic confirmed diagnosis of AGA or FAGA (12 men: II-III Hamilton-Norwood; four women: I-4, II-1 Ludwig) and 16 controls (12 men and four women) (Table 1). Patients in treatment with minoxidil and/or finasteride, with diagnosis of systemic diseases such as hypothyroidism, PCOS (polycystic ovary syndrome), taking medications associated with hair loss and other forms of alopecia such as telogen effluvium, alopecia areata, trichotillomania were excluded. Two 3-mm scalp biopsies were collected from each subject (affected area and occipital auto-control). The expression levels of the *PTGDR2*, *PTGDS*, and *PTGES* were analyzed.

No differences in the expression of these 3 genes were observed between men and women (Figures 1a, 2a and 3a). In the gender subanalysis, overexpression of *PTGDS* was found in men with AGA versus controls (p = 0.002, Figure 1b). *PTGES*

expression was increased in men with AGA compared to controls (p = 0.032, Figure 2b). No differences were found for *PTGDS* nor *PTGES* in women (Figure 1c, 2c). No statistical differences were found in the expression of *PTGDR2* in men or women comparing affected and unaffected areas (Figure 3b-c).

Garza et al. described overexpression of prostaglandin synthase (PTGDS) on baldness areas and its product, the prostaglandin D2 (PGD2), as an inducer of the premature catagen phase. [1] PGD2 (Prostaglandin D2) activity is mediated by the prostaglandin D2 receptor PTGDR2 (GPR44) [1, 2] A Mantel *et al*. suggested that ROS (reactive oxygen species)-driven function in hair follicles keratinocytes is the molecular mechanism by which PGD2 induced testosterone synthesis [3]. Induction of ROS by PGD2 is attributed to 15-deoxy-delta-12,14-prostaglandin J2 (15d-PGJ2), a spontaneous electrophilic metabolite of PGD2 [4, 5]. Therefore, high PGD2 levels found in the bald scalp of AGA may lead to increased testosterone, which can be converted locally to dihydrotestosterone by 5a-reductases to induce AGA.

It has been suggested that inhibitors of PTGDR2 may reverse hair growth through inhibition by PGD2 activity[6]. A multicenter, randomized, double-blind, placebo-controlled, Phase 2A study of setipiprant (oral PTGD2 receptor antagonist) 500 mg tablets BID in AGA is being performed (ClinicalTrials.gov Identifier: NCT02781311). It is interesting that this receptor is not overexpressed in our patients. Perhaps research on treatment should focus on drugs that target PTGDS activity and not PTGDR2.

PTGF2 (prostaglandin F2) and PTGE2 (prostaglandin E2) act synergistically in hair follicles, resulting in hair growth and elongation of the anagen phase [7, 8], antagonizing PTGD2. We found that men patients with early stages of AGA overexpress *PTGES*, the enzyme that synthesizes PTGE2. These results are contrary to those reported in the literature, which reports that *PTGES* is less expressed in patients with AGA. Similar results with other genes involved in AGA, such as *WNT7A*, *CASP7*, *TNF* and DKK1 were overexpressed in areas of alopecia in patients with AGA in early stages of the disease [9, 10]. We hypothesized that this could be due to a negative feedback mechanism at the early stages of AGA, where PTGES is stimulated in an attempt to compensate hair loss.

Herein, we found that *PTGDS* is overexpressed in AGA and *PTGES* is overexpressed in the first stages of AGA. We did not find differences in *PTGDR2* in affected and unaffected individuals. Perhaps, the roll of prostaglandins differs from first to late

stages, resulting in different clinical response to therapy with drugs that target *PTGDR2*, *PTGDS* and *PTGES* depending on the stage of AGA.

Conflict of Interest Statement

The authors state no conflict of interest.

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Table 1. General characteristics of patients included in the study.

Characteristic	**Cases (median, range), *n*:16**	**Controls (median, range), *n*:16**	***p***
Age			0.008
Men	27 (21-28)	23 (21-26)	
Women	44 (39-57)	23 (23-24)	
Case patients			
Men patients with AGA	*Cases, n (%)*	*Women patients with FAGA*	*Cases, n (%)*
Hamilton-Norwood		Ludwig	
II	5 (41.7)	I-4	3 (75)

III	7 (58.3)	II-1	1 (25)

AGA, androgenetic alopecia; FAGA, female androgenetic alopecia.

*chi-square test.

Figure 1. *PTGDS*, *PTGES* and *PTGDR2* (*GPR44*) comparison between expression of AGA and FAGA vs. controls

***Expression of *PTGDS*.** a) Men vs. women (p = 0.519); b) Men: AGA vs. control (0.0.002); c) Women: FAGA vs. control (p = 0.76). ***Expression of *PTGES*. a**) Men vs. women (p = 0.793); b) Men: AGA vs. control (p = 0.0.032); c) Women: FAGA vs. control (p = 0.172). *** Expression of *PTGDR2* (*GPR44*).** a) Men vs. women (p = 0.556); b) Men: AGA vs. control (p = 0.824); c) Women: FAGA vs. control (p = 0.09). An unpaired Student's t-test was performed.

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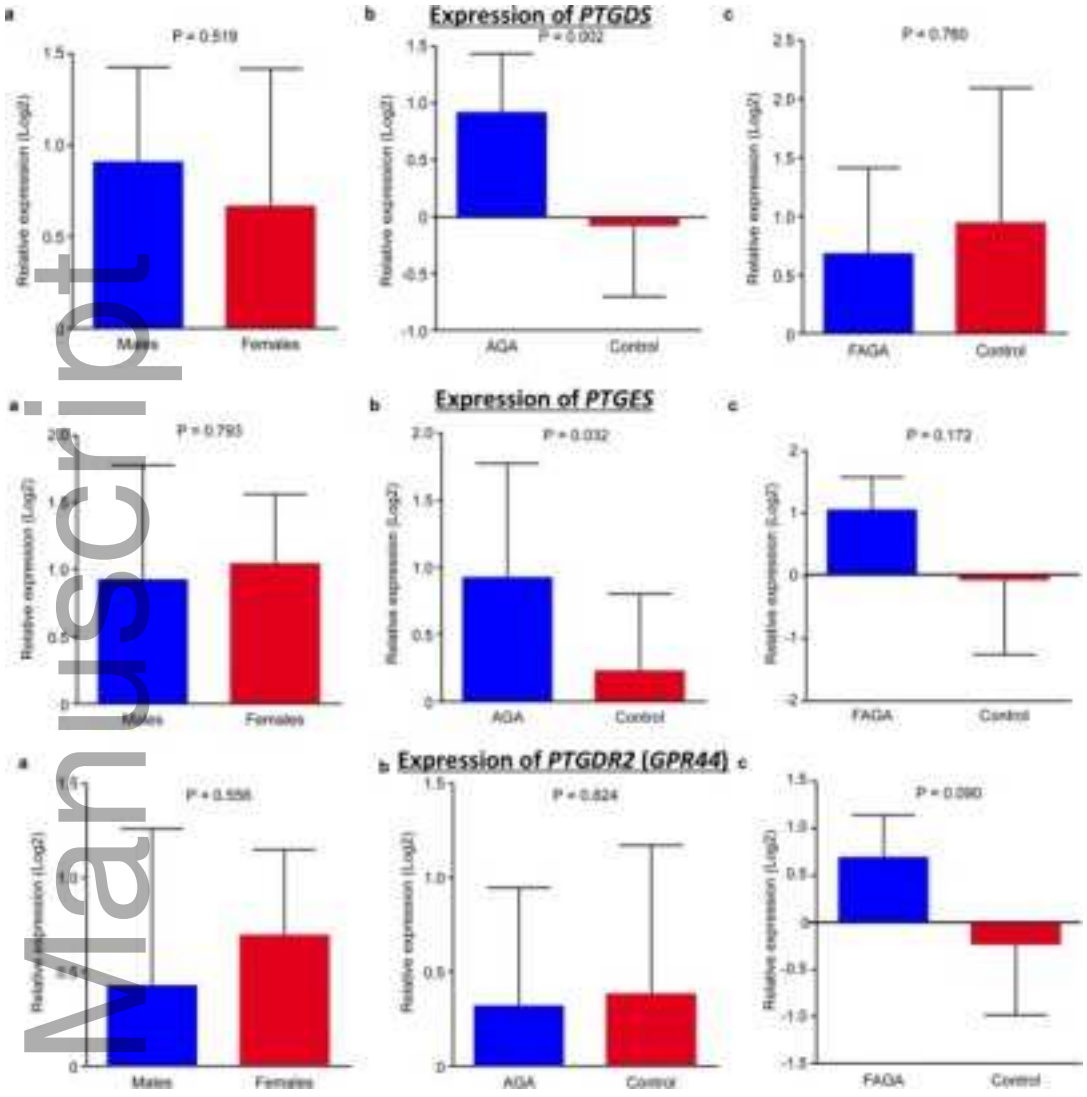

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