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Genetic variant influence on whorls in fingerprint patterns

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To the Editor

Early work on dermatoglyphics identified three major categories of fingerprint patterns: arches, whorls, and loops, differentiated according to landmark structures formed by dermal ridges: the triradii and core (Holt, 1968). These pattern formations are determined by the ratio of volar pad height to width *in utero* (Mulvihill and Smith, 1969) influenced by gene interaction with intra-uterine environment (Penrose, 1968). Mathematical models suggested for dermatoglyphic development include heterogeneous genetic factors influencing development versus between-digit differences, with a pattern of covariation between digits suggestive of a morphogenetic field effect(Martin *et al.*, 1982). Multivariate linkage analyses revealed a pattern of factor loadings for ridge count which supported this argument, and also found linkage to 5q14.1 driven by index, middle and ring fingers (Medland *et al.*, 2007a). A very high heritability (h^2 = .65-.96) has been reported for up to 12 dermatoglyphic characteristics (Machado *et al.*, 2010), suggesting a genetic basis for pattern type. Building on previous findings, the present study sought to identify genetic variants associated with fingerprint patterns on each digit. Two samples of twin and families were recruited from the

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Conflict of interest
The authors state no conflict of interest

Study carried out in Brisbane, Queensland, Australia and Bristol, United Kingdom.

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Queensland Institute of Medical Research (QIMR), and from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study(Boyd *et al.*, 2013). Participants and participant's parents provided written informed consent and ethical approval was obtained from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

Adult and adolescent samples from QIMR were analyzed as one sample of 3301 participants from 1764 families. Fingerprints were collected for the adult sample using rolled ink prints on paper and an electronic archiving system (Medland *et al.*, 2007b) was developed for the adolescent sample. Pattern intensity (the number of triradii) and ridge count (for whorls, the greater of two counts was used) were then manually coded (by SEM and DZL). Within the ALSPAC cohort, 5339 individuals who had GWAS and finger pattern information were used in this paper (please note the study website contains details of data available through a fully searchable data dictionary, http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Pattern type for each digit was scored and coded (by SEM) from photocopies of the palmar surface of the hands (Medland *et al.*, 2010). Any digit where the fingerprint pattern was not clearly visible was coded as missing information. As the full patterns of the thumbs were not clearly visible we excluded this digit from analyses. Intensity and ridge count data were then re-coded in terms of presence or absence of whorls and arches on each digit, with loops as the reference category as they are the most common pattern type, and arches were not analyzed due to low pattern frequency. For reference, the thumb on each hand is coded 1 and the little fingers 5, and right/left hand designated using the prefix L or R. After quality control, 10 variables were included in the study: presence of whorls across all digits (L1-5, R1-5), except L1 and R1 for the ALSPAC cohort and L4, L5, R4, and R5 in the QIMR adult sample.

Both QIMR and ALSPAC samples were imputed using the Hapmap2 r22.36 CEU reference. SNPs that had a minor allele frequency (MAF) of >.01 and could be imputed with confidence (R^2>0.3) were used in these analyses. Only genotyped SNPs were used for chromosome X.

Heritability estimates were conducted in OpenMX (Boker *et al.*, 2012), using binary coded data from the QIMR dataset and with sex as a covariate (Table S1). Principal components analysis (PCA) with Varimax rotation was performed to investigate latent factors within phenotypes after orthogonal transformation of correlations. Results showed 3 underlying components of pattern type: whorls on the middle three fingers (digits 2, 3, and 4) on both hands, whorls on the thumbs (digit 1), and whorls on the little fingers (digit 5) (Table S2).

GWAS were conducted using merlin-offline for each digit and each cohort, and combined using Stouffer's Z score method in METAL to calculate meta-analytic p-values(Willer *et al.*, 2010). There was no evidence of systematic inflation in the QIMR (λ= 1.004–1.027) or ALSPAC (λ =1.007–1.034) results (Figures S3-S5) and several genome-wide significant SNPs ($p < 5\times10^{-8}$) were found. As Table S6 shows, univariate GWAS for the QIMR sample yielded genome-wide significant p-values for the SNP rs1523452 ($p = 7.12\times10^{-9}$) and adjacent SNPs rs 2244503 ($p = 1.52\times10^{-8}$), rs796973 ($p = 5.47\times10^{-8}$), and rs17071864 ($p = 5.42\times10^{-8}$) for the WL5 phenotype. These were independently replicated in the ALSPAC sample (rs1523452, $p = 1.60\times10^{-20}$; rs2244503, $p = 3.76\times10^{-19}$; rs796973, $p = 2.15\times10^{-20}$;

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rs17071864, p = 5.68×10^{-20}) and are encompassed by a single gene *ADAMTS9-AS2* (Figure S7). As Figure 1 shows, these signals were strengthened in meta-analysis. SNPs within a 2 kbp intergenic region downstream of *TBX3* and upstream of *MED13L* within chr12 were also genome-wide significant for WL4 and WR4, peaking at rs1863718 (p = 8.04×10^{-9} and 1.36×10^{-8} respectively), and a variant within the *OLA1* gene region was significant for WL2 (rs10201863, p = 3.46×10^{-8}). To further explore variants at a gene level, gene-based tests were conducted using GATES procedure on KGG2.5 (Li *et al.*, 2011) (Table S8).

Amongst these hits, *ADAMTS9-AS2* and *OLA1* are documented oncogenes, affecting underexpression of glioma with high WHO grade (III/IV) tumors (Yao *et al.*, 2014) and inhibition of *in vitro* cell migration for breast cancer cell lines (Zhang *et al.*, 2009) respectively, suggesting genetic factors regulating dermatoglyphic morphogenesis may also be present in subtypes of cancer. Furthermore chr12 hits between 113904923 – 113903069bp are located in an intergenic region close to *TBX3,* which is known to cause ulnar-mammary syndrome. This concurs with previous literature that limb development *in utero* is influential on subsequent fingerprint patterns that emerge (Mulvihill and Smith, 1969).

ADAMTS9-AS2 is an antisense RNA located at 3p14.1, which may be an mRNA inhibitor for the adjacent gene *ADAMTS9*. Although there is no direct explanation of the role of *ADAMTS9-AS2* in development of whorls on the little fingers, RNAseq analyses show high expression in reproductive organs as well as in the colon and lungs, suggesting it may be influential in early organ development. *ADAMTS9* and *OLA1* are also expressed in low to medium levels in the skin. Interestingly, variants in *ADAMTS9-AS2* also appear to influence whorls on all digits to differing levels of significance and variances (Figure 2A, 2B). Allele frequencies at this variant show that the G allele was associated with higher incidence of whorls in digit 5 (Figure 2C).

In conclusion, although this study did not find direct evidence for the effects of single genetic variants on specific fingerprint pattern phenotypes, variants within *ADAMTS9-AS2* show a gradient influence on whorls across all digits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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In memory of Bodgan Mdzewski, who contributed significantly in counting QIMR fingerprint intensity scores.

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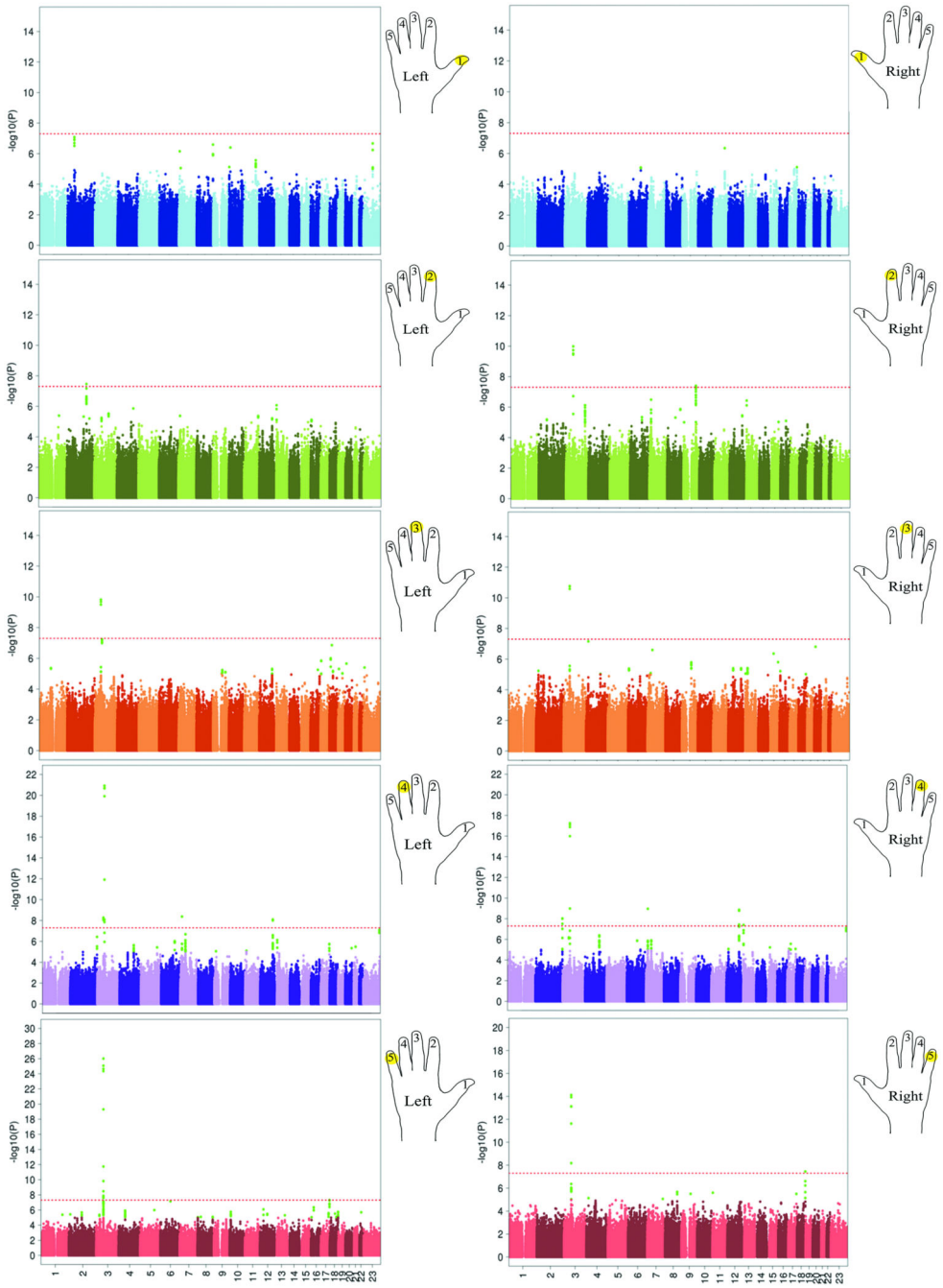

Figure 1. Manhattan plots for meta-analysis results

rs1523452 within the ADAMTS9-AS2 gene region presented the strongest signal for phenotypesWL5 ($p = 9.74\times10^{-27}$) and WR5 ($p = 7.62\times10^{-15}$), accounting for 1.61% and 0.93% of the variance. rs1523452 also influences WL4 ($p = 2.16\times10^{-21}$), WR4 ($p = 1.33\times10^{-17}$), and WR2 ($p = 3.08\times10^{-10}$), attenuating at WL2 ($p = 9.24\times10^{-6}$) and further reduced for WL1 ($p = 2.66\times10^{-5}$) and WR1 ($p = 0.0001$).

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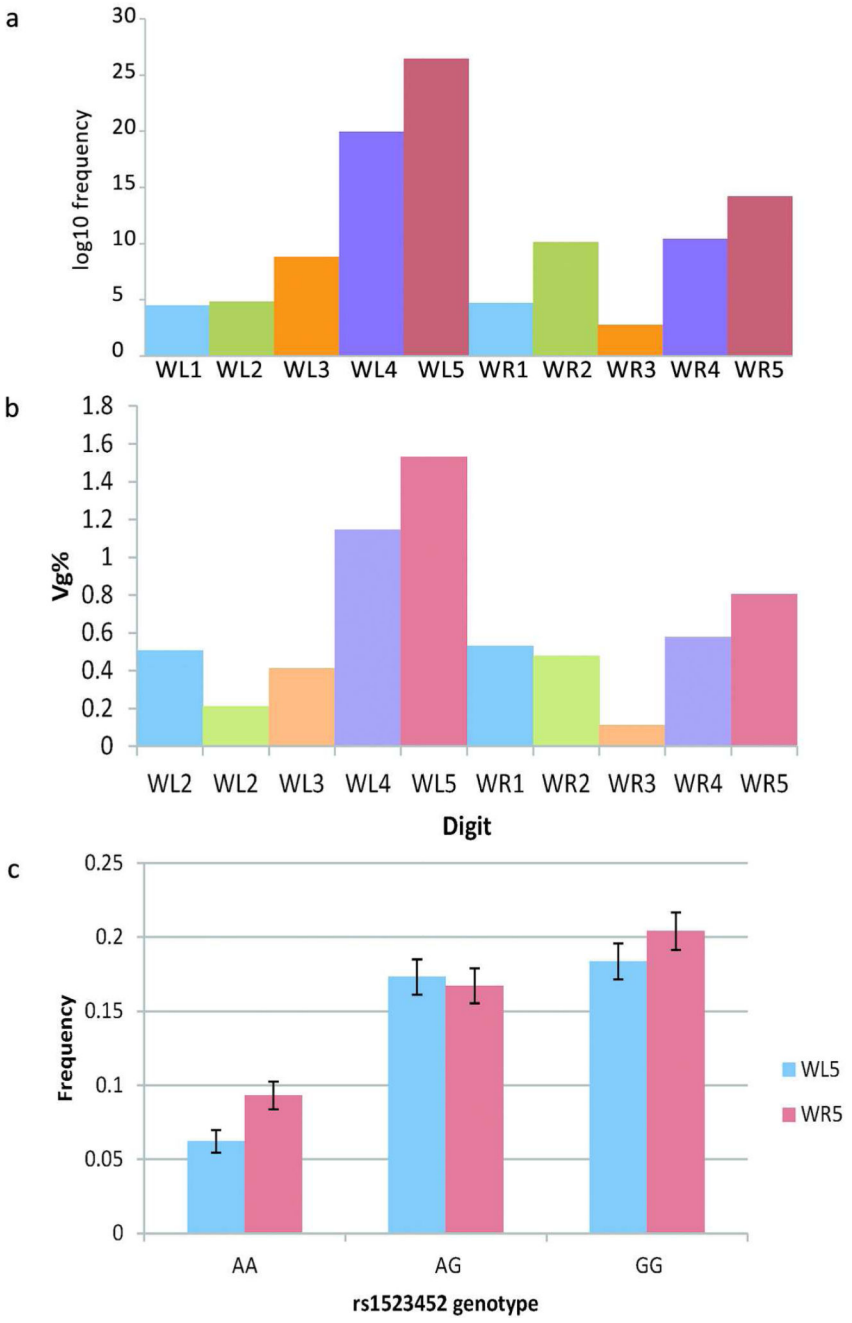

Figure 2.

Histograms of **a**: meta-analyses -log10(p-values) and **b**: % variation explained by rs1523452 (within the ADAMTS9-AS2 gene region) across digits, obtained by $Z^2/(N-2+Z^2)$; **c**: Trait frequency as a function of allelic variation - Frequency of whorls on the left little finger (WL5; blue bars) and right little finger (WR5; red bars) as a function of the genotype rs1523452 in a sample of unrelated individuals from the $QIMR_1$ cohort (n[AA] = 708,

n[AG] = 335, n[GG] = 49). With more G alleles, the proportion of whorls increases. Vertical bars correspond to the 95% confidence intervals on prevalence.

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