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肢体发育相关基因在指纹花纹形成中发挥关键作用——‘一因多效’连接肢体发育和指纹花纹形成

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摘要 肤纹具有长期的实用性和文化性, 且与身俱来, 但人们对其变化背后的机制知之甚少。通过对中国汉族人群的全基因组扫描, 该团队发现了18个与指纹类型相关的基因座, 包括长期以来被认为的中间三枚手指指纹花纹之间的“模式块”相关性的遗传基础。值得注意的是, 该团队发现了*EVI1*基因附近的一个变异, 它可以改变对*EVI1*基因表达的调节活性, 并证实了*Evi1*在小鼠脊线模式中的重要作用。在人类发育过程中, *EVI1*的动态表达支持其在塑造四肢和手指方面发挥作用, 而不是直接影响皮肤模式。多群体的荟萃分析鉴定了43个与指纹相关的位点, 基因显著富集在肢体发育通路中。此外, 指纹花纹与手的比例存在基因上的关联。综上所述, 这些发现支持了肢体发育基因在影响指纹花纹形成中起关键作用。

关键词 指纹花纹; 遗传; 全基因组关联分析; 多群体荟萃分析; 肢体发育; *EVI1*

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Limb Development Genes Underlie Variation in Human Fingerprint Patterns — Pleiotropic Effects of Limb Development and Fingerprint Patterning

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Abstract Fingerprints are of longstanding practical and cultural interest, but little is known about the mechanisms that underlie their variation. Using genome-wide scans in Han Chinese cohorts, this study identified 18 loci associated with fingerprint type across the digits, including a genetic basis for the long-recognized "pattern-block" correlations among the middle three digits. In particular, it identified a variant near *EVI1* that alters regulatory activity and established a role for *EVI1/Evi1* in dermatoglyph patterning in mice. Dynamic EVI1 expression during human development supports its role in shaping the limbs and digits, rather than influencing skin patterning directly. Trans-ethnic meta-analysis identified 43 fingerprint-associated loci, with nearby genes being strongly enriched in general limb development pathways. This study also found that fingerprint patterns were genetically correlated with hand proportions. Taken together, these findings support the key role of limb development genes in influencing the outcome of fingerprint patterning.

Keywords fingerprint pattern; genetics; Genome-Wide Association Study; trans-ethnic meta-analysis; limb development; *EVI1*

前世今生, 奠定肤纹研究重要意义

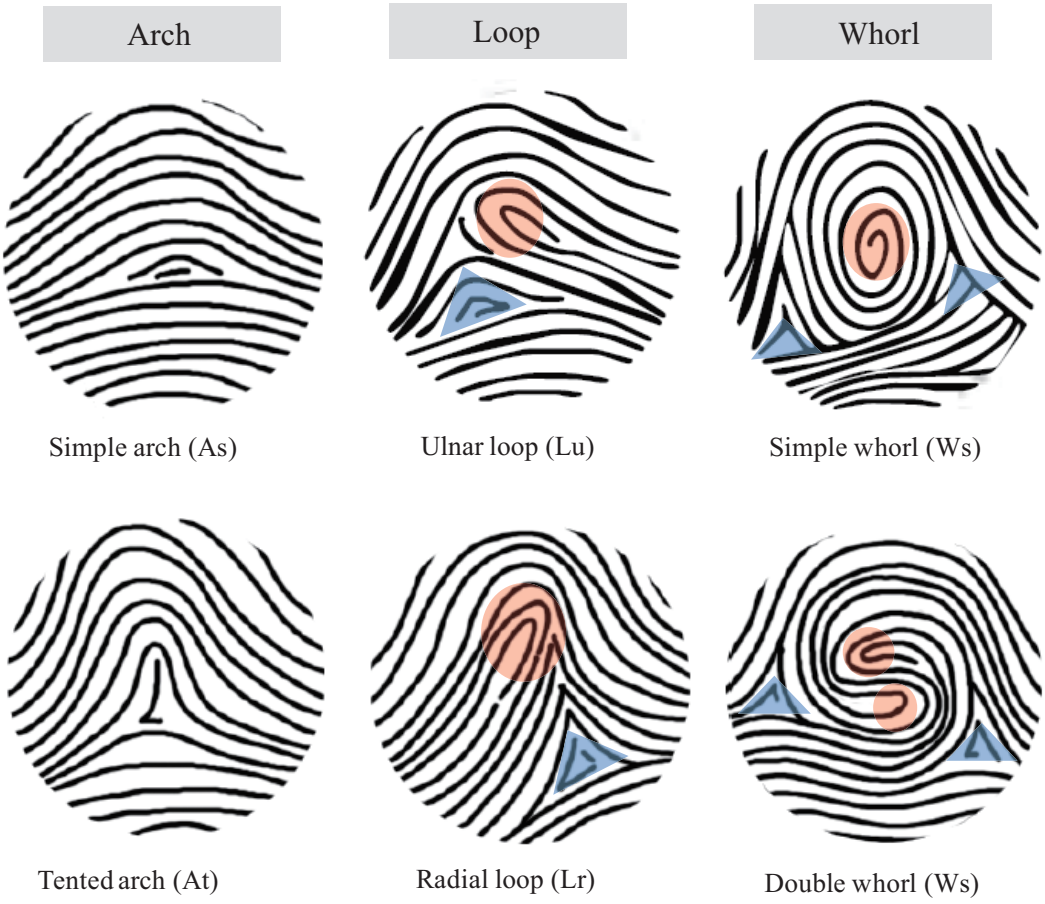
肤纹又称皮纹, 是人类和灵长类动物厚型皮肤的纹理, 即手足掌面由表皮嵴线形成的花纹, 其中分布在指尖处的花纹被称为指纹。 此外, 肤纹还包括掌纹和足纹等[1]。命相学把人的命运与肤纹联系起来, 认为人的寿命、遭遇、婚姻等都可以"算"出来。因此, 正确认识人体肤纹, 是肤纹发展的关键。中国是世界上公认的指纹观察和应用的发源地。我们的祖先观察和应用肤纹的历史已达几千年之久。出土的各类古代陶器、陶罐、青铜器文物上也都有类似指纹的装饰。各类民间契约及断案文书上也能发现指纹的遗迹。这说明我们的祖先已对指纹进行过观察并加以运用。直到近300多年, GALTON[2]总结了人皮肤上的这些纹路, 确立了指纹的个体差异性及持久稳定性, 并于1892年出版了《指纹学》一书, 标志着近代指纹科学理论的开始。1926年, CUMMINS[1,3]和MIDLO[1]对皮肤纹理的各个层面都作了清楚的论述, 从方法学、解剖学到人类学、遗传学以及胚胎学, 规范了皮纹学的定义, 并巧妙地将皮肤(dermato)与雕刻(glyphic)结合成'dermatoglyphics'(皮肤纹理学、肤纹学或皮纹学), 建立了皮纹学理论。也因此, CUMMINS被称为"皮纹学之父", 并于1943年出版了《指纹、手掌和脚掌》一书[4], 该书被认为是肤纹学领域的圣经。 自此, 肤纹学正式成为一个专业的研究领域。

国内外许多学者也在各个领域相继对肤纹学的发展作出了重大贡献。从体质人类学角度, WILDER[5]指出肤纹特征在中国人和日本人间存在差异。之后, RIFE[6]对全球多个国家人群的肤纹总结, 以及张海国[7]在我国不同民族人群中的肤纹调查, 均证实了肤纹具有明显的群体差异性。进而, 张海国等[8]利用肤纹作为遗传标记将我国56个民族分成南方和北方两大群体, 还找到了民族肤纹的标志性群体。由此可见, 肤纹对人类学、民族学、遗传学的研究均有重要意义。1958年, WALKER[9]首次提出可以利用肤纹特征判别唐氏综合征, 证实肤纹可

以作为染色体异常的诊断指标。在之后的二十年间, 肤纹在唐氏综合征辅助诊断中的应用研究得到了大量医生、学者的青睐, 并在REED等[10]的研究中达到高潮。REED等[10]筛选出4项可以明显区分唐氏综合征患者与正常人的肤纹特征, 并构建判别方程, 作为诊断唐氏综合征的简单依据。我们近期也对此项工作进行了进一步探索, 经过更严密的肤纹特征筛选, 将判别准确率提升到了98%, 并将假阴性率控制在了6.6%[11]。除唐氏综合征外, HOLT[12]在《肤纹遗传学》一书中, 总结了对不同人群(包括正常人群和多种先天性疾病患者)手指和手掌纹路的研究。以上, 说明肤纹在医学辅助诊断领域中具有重要应用价值。如今, 肤纹, 尤其是指纹, 凭借其个体独特性以及永久稳定性已被广泛应用于个人认定、侦查破案、信息安全、医学辅助诊断等各个领域中, 横跨法医物证学、生物学、民族学、人类遗传学、医学、计算机科学等各学科。

析理入微, 解析指纹花纹遗传学结构

在指尖上, 有规律的脊线和沟纹形成了三种主要模式的指纹: 弓型、箕型和斗型(图1)。尽管指纹的出现可能是为了帮助抓取[13-14]和表面纹理的触觉感知[15-16], 但自19世纪以来, 指纹因其独特性和永久性而已被广泛用于各领域。妊娠10周后, 手指指尖处在肿胀消退的掌侧垫上的皮肤上开始出现嵴线。到第14周时, 在表皮–真皮交界处初生嵴的构型确定了未来的指纹花纹(弓型、箕型和斗型)的形成[17-18]。人们提出了几种机制来解释这些花纹的形成, 包括基于通过屈曲分解表皮上的机械应变的理论[19-20], 根据血管或神经走向设定的嵴线排列[21], 以及反应–扩散信号过程的影响[22]。然而, 皮肤纹图案和整个指纹花纹形成的生物机制在很大程度上还不清楚。



根据轴三角和中心区域确定指纹花纹类型。有三种主要类型: 弓型、箕型和斗型。每一种按陡度、嵴线方向和中心区域变化为两类亚型。
Pattern-types of fingerprints according to the number of triradii/deltas (triangles) and cores (circles) (STAR methods). There are three main types: arch, loop and whorl. Each main group contains two sub-types according to the steepness, direction of ridges and the variable core.

图1 指纹花纹的类型(根据参考文献[23]修改)

Fig.1 Pattern-types of fingerprints (modified from reference [23])

KARMAKAR等[24-25]和LOESCH等[26]认为绝大多数的肤纹特征都受到多个基因的影响, 并且指出如指纹花纹、总嵴线数等一些特征存在显性遗传的主效基因。但有研究证明指纹花纹也满足多基因遗传模型, 且存在主效基因的影响[27], 其遗传因素的影响占60%~90%, 还存在外界环境的影响[25]。随着对人体皮纹分析更加精细, 样本量不断增加, 有学者通过全基因组关联分析(Genome-Wide Association Study, GWAS)的方式, 定位到几个与欧洲血统群体的指纹花纹相关的基因座[28], 但这些基因座此前都没有被报道参与肢体或皮肤发育的功能, 学者们对潜在的生物学机制几乎没有深入了解。基于指纹花纹在不同种族群体中, 甚至不同手指上外显率的不同, 我们认为在不同种族不同手指上的主效基因对肤纹特征的影响应该是存在差别的, 对肤纹特征背后遗传因素的探索还任重而道远。

针对这一问题, 我们从定位与指纹花纹表型相关的遗传变异入手, 通过对23 000多例个体进行全基因组关联扫描与多群体荟萃分析, 从中识别出43个与人类指纹花纹相关的遗传基因座(图2A)。这些基因座在欧亚不同祖先群体中存在一定差异(图2B), 但总体相同, 这可能是由于不同的等位基因效应大小或频率不同造成的。这些与指纹花纹相关的基因显著富集在肢体发育与形成的相关通路上, 而非皮肤发育相关通路上(图2C)。

值得注意的是, 我们的研究确认了左右中间三枚手指指纹花纹间存在“模块现象”(图3A和图3B), 即中间三枚手指指纹高度相关[29-31]。而位于3q26.2区域邻近*EVI1*基因的变异位点与中间三枚手指指纹的复合表型显著相关, 这为上世纪即被发现的“指纹模块现象”提供了表型组学和遗传学解释(图3C)。

基于小鼠动物模型和人胚胎组织的实验观察发现, 人类胎儿组织在从肢体发育到皮纹形成的系列过程中, 支持*Evi1/EVI1*基因发挥塑造四肢和手指作用的, 正是表达于肢体发育期的间充质细胞, 而非皮肤发育期的上皮细胞(图4)。这进一步与研究结论相印合: 指纹相关基因通过调控肢体发育来影响指纹花纹的形成。

此外, 通过多表型关联分析发现, 指纹花纹与手指长度比例特征间紧密相关, 两者共有相同的遗传基础。如小指相对越长, 掌长相对越短, 双手斗型花纹越多; 而食指远端指节(指纹形成处)相对越长, 斗形花纹则越少(图5)。

前景广博, 助力识别潜在疾病风险

肤纹在早期胚胎发育阶段形成, 出生后便不再改变[2]。而在表皮嵴发育阶段, 研究发现皮肤内已经出现了血管神经对, 其与肤纹发育处于同一时期。当肤纹发育不全或发育异常时, 常伴有神经等的发育异常[32]。CUMMIN[33]首次于1936年观察到唐氏综合征患者的肤纹出现异常, 如通贯手(断掌), 从而开创了医学皮肤纹理学的研究。之后一系列研究也发现肤纹和染色体畸变综合征、单基因疾病等都有着密切联系[34-37]。我们研究所揭示的影响指纹花纹形成的是一系列肢体发育相关的重要基因, 这些基因在人体发育中往往起着重要的‘一因多效’作用, 为肤纹与人体其他表型与疾病的关联研究提供了重要理论基础。通过肤纹特征和先天遗传病间的统计分析, 筛选出患者的最佳皮肤纹理特征组合, 有望运用在新生儿先天性疾病的早期筛查中, 从而实现早诊断、早治疗。

范式革新, 展现人类表型组学创新策源重大意义

人类表型组, 是人体所有生物特征的集合。开展人类表型组研究一个很重要的目的, 就是要发现基因–表型–环境之间以及宏观–微观表型之间的关联机制, 尤其是“强关联”及其背后的机制。基于人类表型组计划“测一切之可测”的理念, 量化相当规模的志愿者肤纹特征, 并寻找其与其他表型或疾病之间的关系, 进而发现并解析表型之间的强关联, 尤其是那些现在科学家还没有注意到的、与人类健康息息相关的表型间的强关联, 最终形成一张由各种强关联组成的“导航图”, 为未来的生命健康研究提供新的指引和方向。

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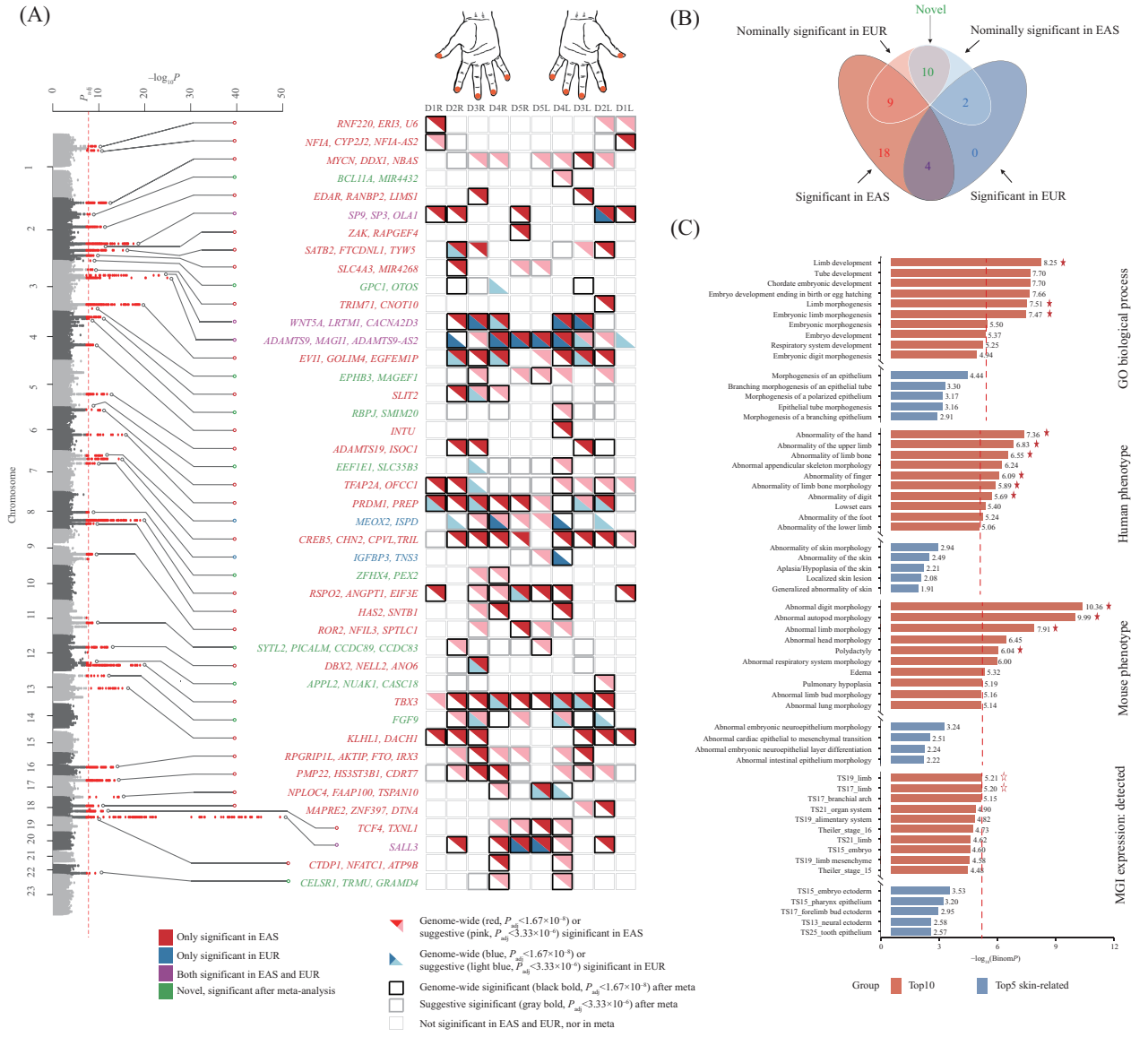
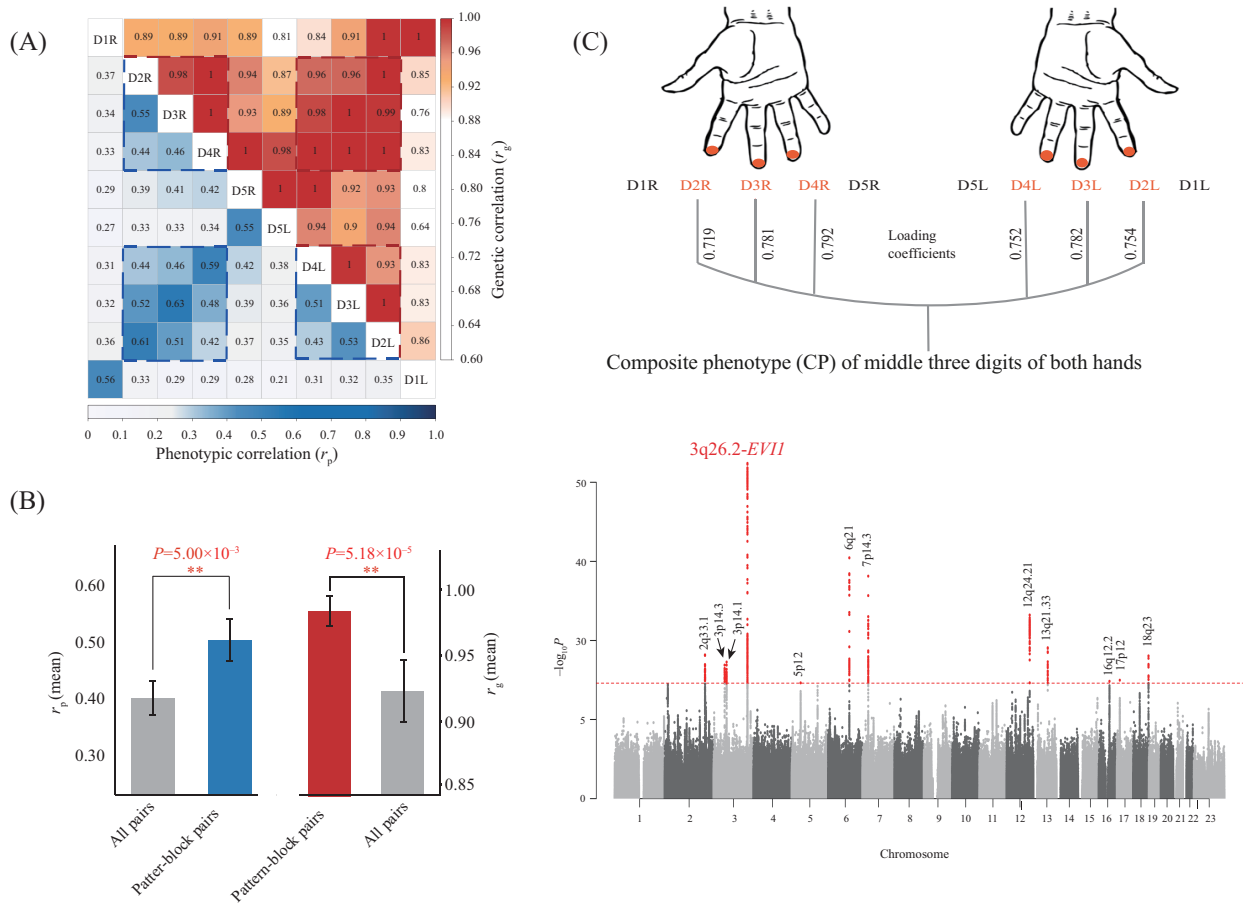


A: 曼哈顿图显示了欧(European, EUR)、亚(East Asian, EAS)不同祖先群体十枚手指上指纹花纹的荟萃分析结果。有43个信号与至少一个手指上的指纹模式相关(P_{adj}<1.67×10^{-8}), 不同颜色的基因名称: 紫色表示EAS和EUR均显著; 红色和蓝色分别表示仅在EAS和EUR中显著; 绿色表示在EAS或EUR中均不显著, 但只有在合并两者的荟萃分析后才显著。粗体基因显示与肢体表型发育异常相关。右侧的块图表示左侧信号对应的手指。红色和蓝色三角形分别代表EAS和EUR显著性, 而深色和浅色分别代表达到Bonferroni校正后全基因组显著性的信号(P_{adj}<1.67×10^{-8})和边际显著性水平的信号(P_{adj}<3.33×10^{-6})。 在多群体荟萃分析后, 粗体框表示全基因组显著(黑色)或边际显著(灰色)。B: 韦恩图显示与指纹花纹相关信号在各群体中的分布。C: 与指纹花纹相关的43个基因功能注释。红色星号表示经Bonferroni校正后基因显著富集的肢体相关条目(红色虚线)。只显示富集分析后排名前10位的条目和前5位上皮/皮肤相关的条目。

A: a Manhattan plot showing the results of the meta-analyses combining GWAS of East Asian (EAS)-ancestry (TZL, NSPT, JD, CKB and WeGene) and European (EUR)-ancestry cohorts (ALSPAC, QIMR and Pittsburgh) across all ten digits (D1L/R were unavailable in JD and ALSPAC). There were 43 signals associated with fingerprint patterns of at least one digit (P_{adj}<1.67×10^{-8}), with gene names in different colors: purple indicating significant in both EAS and EUR; red and blue indicating only significant in EAS and EUR, respectively; green indicating not significant in either EAS or EUR, but only significant after the meta-analysis combining both. Bold genes showed associations with limb phenotypes abnormalities. The block map on the right represented the digits corresponding to the signals on the left. Red and blue triangles indicate significance in EAS and EUR, respectively, while dark and light colors represented signals that reached the adjusted genome-wide significant (P_{adj}<1.67×10^{-8}) and suggestive levels (P_{adj}<3.33×10^{-6}), respectively. Bold frame indicated genome-wide significant (black) or suggestive (gray) significant after combined meta-analyses. B: venn diagram summarizing fingerprint-associated signals. C: enrichment of annotations across ontologies for the 43 fingerprint-associated signals. The red asterisk indicates limb-relevant terms that genes are significantly enriched in after Bonferroni correction (the red dotted lines). Only the top 10 terms ranked after enrichment analysis and top 5 epithelial/skin-related terms are shown.

图2 多群体荟萃分析发现指纹花纹相关信号在肢体发育相关通路中显著富集(根据参考文献[23]修改)

Fig.2 A meta-analysis of fingerprint patterns showing signals enriched in limb development (modified from reference [23])



A: 十枚手指指纹花纹两两间表型相关分析(蓝色)和遗传相关分析(红色)均表明左右中间三枚手指指纹花纹存在“指纹模块现象”(n=9 909)。虚线框表示两只手的同名手指与相邻手指上指纹花纹之间的高度相关性。 图中由高到低的相关性分别用颜色和相关系数(r)表示。B: 左右中间三枚手指之间的指纹花纹的相关性(Pattern-block pairs)高于十枚手指的所有随机对之间的相关性(all pairs)。C: 对从左右中间三枚手指的指纹花纹中提取的复合表型进行全基因组关联扫描。复合表型对6个相关变量的加载系数在0.719~0.792。

A: “Pattern block” phenomenon of the middle three digits on both hands revealed by pair-wise phenotypic correlation (blue) and genetic correlation (red) among the ten digits (n=9 909). The dashed box indicates high correlations between the same digits of both hands and neighboring digits. The correlations from high to low were represented by both color and correlation coefficients (r) in the figure. B: the correlations of fingerprint patterns between the middle three digits on both hands (Pattern-block pairs) are higher than the correlations of all random pairs of the ten digits (all pairs). C: genome-wide scan on the composite phenotype extracted from the fingerprint pattern of the middle three digits on both hands. The loading coefficients of the composite phenotype on the six correlated variables are between 0.719 and 0.792.

图3 *EVI1*附近位点可能为左右中间三枚手指指纹花纹“模块现象”的遗传基础(根据参考文献[23]修改)

Fig.3 The top signal near *EVI1* may be the genetic basis of the middle three digit “Pattern-block” phenomenon (modified from reference [23])

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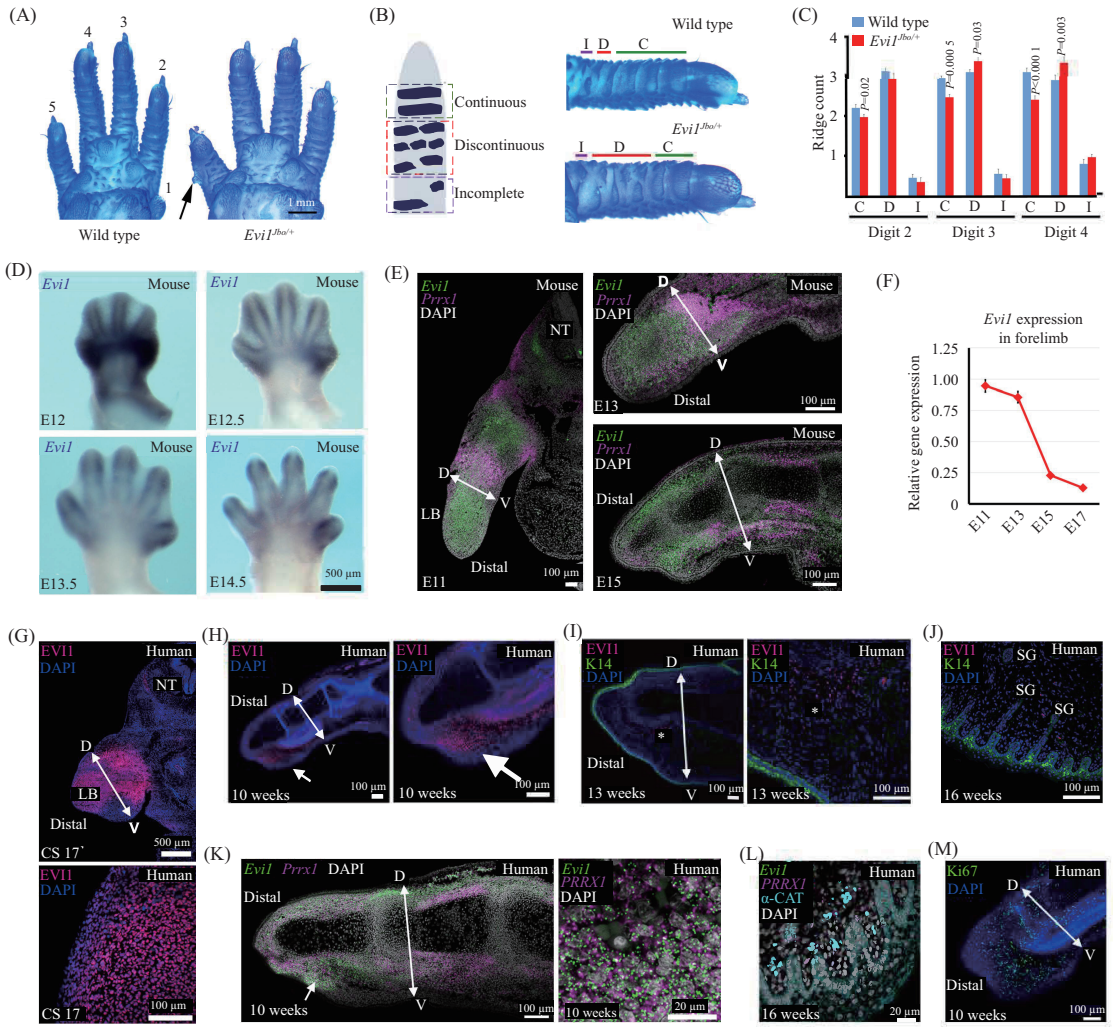
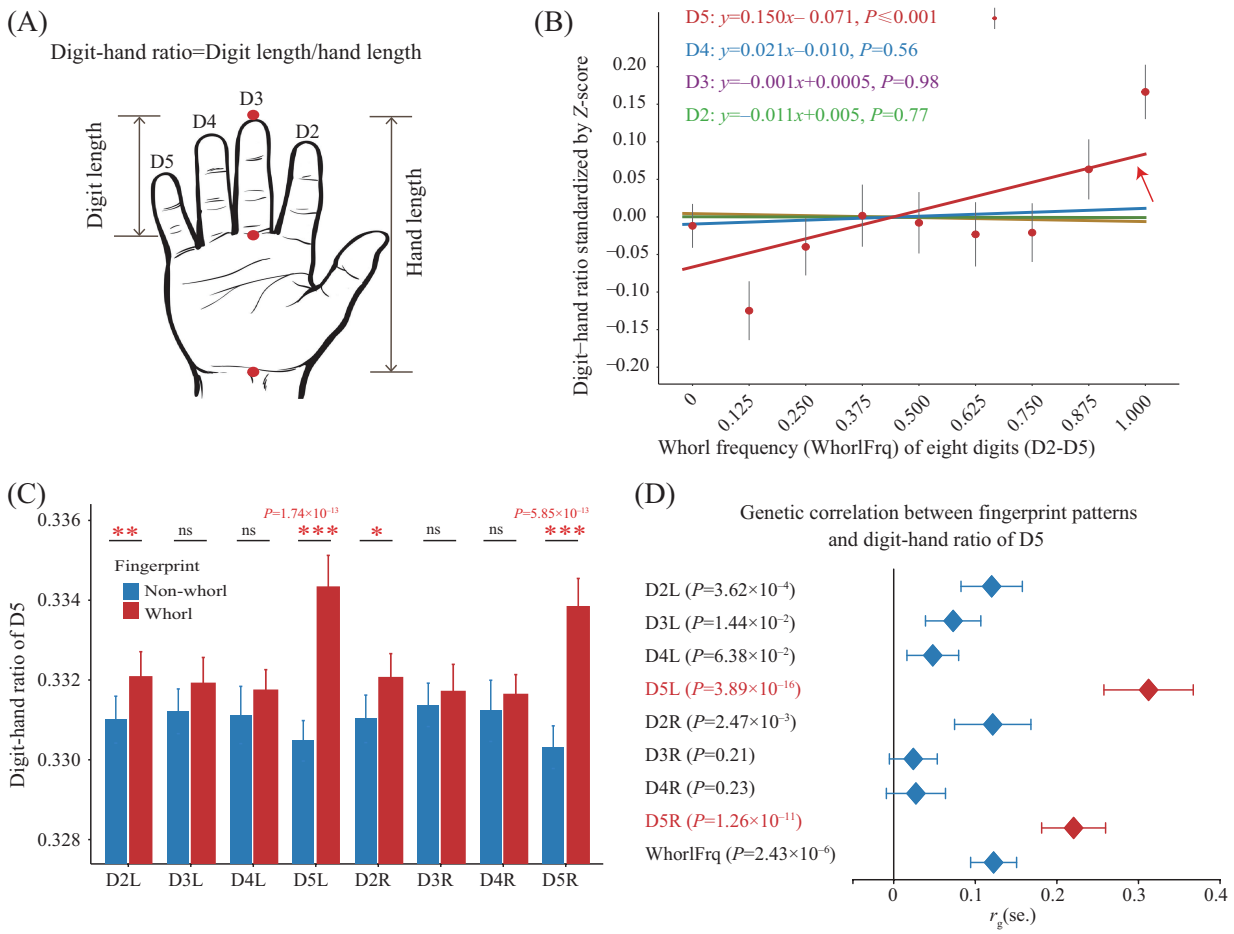


A: 野生型和*Evi1*$^{Jbo/+}$成年小鼠甲苯胺蓝染爪掌真皮表面显示皮纹构型。箭头表示突变小鼠爪子上额外D5指。B: 野生型和*Evi1*$^{Jbo/+}$小鼠D4指和腹侧横脊分类示意图。表示携带连续的C、不连续的D和不完整的I脊的区域。C: 野生型和*Evi1*$^{Jbo/+}$突变体的指脊模式定量分析。在所有突变趾上, 连续脊减少, 而D3和D4携带更多的不连续脊。D: 整体原位杂交检测小鼠胚胎前肢*Evi1*的表达。腹侧视图。E: RNAscope原位杂交检测小鼠胚胎肢体和指肢E11.5和E17.5之间的*Evi1*和肢体间质标记物*Prrx1*转录物。F: 定量RT-PCR检测小鼠前肢E11.5(全肢芽)、E13.5、E15.5和E17.5(仅限同源体)时*Evi1*的表达。G~J: 免疫荧光检测人胚胎组织中EVI1的表达。CS17胚胎(约6周EGA)横切面显示肢芽间充质细胞(下方放大图)的核表达(G)。神经管(NT)指背侧中线。H: 10周EGA手指纵切面, 箭头表示指纹形成的凸起掌侧垫。13周EGA(I)指和16周EGA(J)指检测*EVI1*和上皮标志物K14。虚线表示真皮–表皮交界处。*表示血细胞自身荧光。SG为汗腺。K、L: RNAscope原位杂交在单细胞中检测10周EGA(K)和16周EGA(L)人类手指的*EVI1*和*PRRX1*表达。M: 10周EGA手指增殖细胞标志物Ki67的检测。背轴(D)和腹轴(V)标注, 核用DAPI染色。误差线表示标准误差。

A: palmar dermal surface of toluidine blue stained paws from wild type and *Evi1*$^{Jbo/+}$ adult mice showing dermatoglyph arrangement. Arrow indicates spur on the mutant digit 5 (D5). B: schematic depicting transverse ridge categories on mouse digits and ventral surface of D4 of wild type and *Evi1*$^{Jbo/+}$. Regions carrying continuous C, discontinuous D, and incomplete I ridges are indicated. C: quantification of digit ridge pattern in wild type and *Evi1*$^{Jbo/+}$ mutants. Continuous ridges are reduced on all mutant digits, while D3 and D4 carry more discontinuous ridges. D: wholemount *in situ* hybridization detecting *Evi1* expression in mouse embryonic forelimbs. Ventral view. E: RNAscope *in situ* hybridization detecting *Evi1* and the limb mesenchyme marker *Prrx1* transcripts in mouse embryonic limb and digits between E11.5 and E17.5. F: quantitative RT-PCR determination of *Evi1* expression in mouse forelimb at E11.5 (whole limb bud), E13.5, E15.5 and E17.5 (autopod only). G-J: immunofluorescence detecting EVI1 expression in human embryonic tissue. Transverse section of CS17 embryo (~6-week EGA) shows nuclear expression in mesenchymal cells of the limb bud (LB, magnified in lower panel). The neural tube (NT) indicates the dorsal midline (G). Longitudinal section of 10-week EGA digit, arrow indicates the raised volar pad across which fingerprints form (H). 13-week EGA digit (I) and 16-week EGA digit (J) detecting EVI1 and epithelial marker K14. Dotted line indicates dermal-epidermal junction. * indicates cateinin immunofluorescence. SG: eccrine sweat gland. K,L: RNAscope *in situ* hybridization detecting *EVI1* and *PRRX1* transcripts in sectioned 10-week EGA (K) and 16-week EGA (L) human digit. Individual cells co-express *EVI1* and *PRRX1*. Asterisks indicates autofluorescent blood cells. M: detection of proliferative cell marker Ki67 in 10-week EGA digit. Dorsal (D) and ventral (V) axes are annotated: Nuclei are stained with DAPI. Error bars indicate S.E.M.

图4 检测小鼠皮肤纹路和肢体发育过程中EVI1的表达(图片来源参考文献[23])

Fig.4 EVI1 in dermatoglyph patterning and limb development (image source from reference [23])



A: 手和手指长度示意图, 指手比(DHR)是指手指长度与手长度的比值。B: 斗型花纹出现频率与各手指DHR的相关性。使用*Z*分数来标准化左手和右手的平均DHR。 红点表示平均值, 短黑线表示每组的标准差。 箭头表示线性回归通过显著性检验。C: 各指斗型花纹与平均DHR值关系条形图。误差线表示标准误差。*P<0.05, **P<0.01, ***P<0.001。D: 各指斗型花纹与平均DHR值的遗传相关性。使用GCTA软件的双变量GREML进行估计和检验。误差线表示标准误差。

A: diagrammed human hand with measured phenotypes, including hand and digit length. The digit-hand ratio (DHR) is the ratio of digit length and hand length. B: the association between the whorl frequency of eight digits (D2-D5) and the DHR of each digit. We used *Z*-score to standardize the mean DHR of left and right hands. Red dots indicate the average values and short black lines the standard deviation for each group. The arrow indicates the linear regression passes the significance test. C: bar plot of fingerprint patterns of each digit (D2-D5) and the mean DHR of D5. Error bars indicate S.E.M. *P<0.05, **P<0.01, ***P<0.001. D: genetic correlations between fingerprint patterns and the mean DHR of D5. Estimates and tests were performed using the bivariate GREML of GCTA software. Error bars indicate S.E.M.

图5 指纹花纹和手征间关系(n=6 318)(图片来源参考文献[23])

Fig.5 Association between fingerprint patterns and hand phenotypes (n=6 318) (image source from reference [23])

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