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Effects of destrin pathway mutations on the gene expression profile

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ABSTRACT. This study aimed to explore the interaction and crosstalk between pathways in response to destrin mutations. All the pathways from the MINT database were downloaded, a protein-protein interaction network was then constructed, and the crosstalk between pathways was investigated, in particular, the overlap of 2 significant pathway analysis results. As expected, the results showed that regulation of the actin cytoskeleton was the significant pathway of destrin mutations in mice. Further analysis indicated that 28 significant pathways cross-talked with the pathway regulating the actin cytoskeleton. Importantly, 3 pathways, including regulation of actin cytoskeleton pathway, pathways in cancer, and the B cell receptor signaling pathway were linked by inositol phosphate metabolism based on crosstalk analysis of Gene Ontology relationships among pathways. All of these pathways have been demonstrated to participate in cytoskeleton dynamics. These findings might provide valuable insights into cytoskeleton dynamic abnormalities in destrin mutations of corneal diseases.

Key words: ADF/Cofilin; Cytoskeleton dynamics; Pathway crosstalk

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INTRODUCTION

Corneal disease is responsible for 6% of legal blindness in the United States and is frequently the main cause of bilateral blindness in the world, second only to cataract (Ikeda et al., 2003; Li et al., 2009). Visual loss in many corneal diseases is due to changes in the morphology and function of the corneal epithelial surface, including cell hyperproliferation, inflammation, and angiogenesis (Dawson et al., 2009).

Destrin (also known as actin-depolymerization factor, ADF) is an essential actin regulatory protein of the ADF/cofilin family that binds to the actin subunits of filamentous actin (F-actin), enhancing the subunit off-rate and promoting filament severing. Thus, this family of proteins is responsible for increasing the turnover of actin filaments and is involved in the regulation of cytoskeleton dynamics (Tokuraku et al., 2001; Maciver and Hussey, 2002). Dstn^{corn1} mice represent a spontaneous mutant line that exhibits ocular surface abnormalities shortly after birth and therefore often serves as a good model to study corneal disease. The histology of Dstn^{corn1} corneas showed that the hyperplastic corneal epithelium expressed an increased level of keratin 14 and involucrin, while the level of keratin 12 was not altered (Zhang et al., 2008). The normal cornea is deficient in blood and lymphatic vessels to maintain corneal transparency, unless severe inflammatory or other strains cause a disruption of the antiangiogenic privilege of the cornea. It has been shown that hemangiogenesis and lymphangiogenesis in the Dstn^{corn1} cornea depend on vascular endothelial growth factor receptor 3 (VEGFR3) signaling (Cursiefen et al., 2005). Recent reports have suggested that vascularization of Dstn^{corn1} corneas arises from the lack of soluble VEGFR, sflt-1, which has been proposed as an essential factor for maintenance of avascularity in a normal cornea. Suppression of endogenous sflt-1 by neutralizing antibodies, RNA interference, or Cre-lox-mediated gene disruption abolishes corneal avascularity in mice, but recombinant sflt-1 administration restores corneal avascularity in corn1 and Pax6+/- mice (Ambati et al., 2006).

Genome-wide screening of differentially expressed genes (DEGs) in the cornea of Dstn^{corn1} mice reveals that the expression of a large portion of genes associated with cytoskeletal dynamics was up-regulated (Verdoni et al., 2008). Nearly half of these genes are targets of the serum response factor (SRF), an essential regulator of the actin cytoskeleton (Miano et al., 2007; Miano, 2008). The conditional ablation of Srf in the corneal epithelium of a diseased Dstn^{corn1} cornea results in the rescue of epithelial cell hyper-proliferation, inflammation, and neovascularization phenotypes (Verdoni et al., 2010). These results indicate that there is an underlying interaction among these DEGs. Given the complex nature of biological systems, pathways often need to function in a coordinated fashion to produce appropriate physiological responses to both internal and external stimuli (Li et al., 2008). Therefore, we performed research on the protein-protein interaction (PPI), significant pathway, and crosstalk between pathways based on the previous study in our institution, with the hope to lay an important theoretical foundation for understanding the molecular mechanism of destrin in corneal diseases.

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MATERIAL AND METHODS

Data sources

We download all the pathways from KEGG (Kyoto Encyclopedia of Genes and Genomes) (Kanehisa, 2002) and all the PPI datasets from MINT (the Molecular Interaction da-

tabase) (Ceol et al., 2010), which contains the mouse PPI datasets from IntAct (Aranda et al., 2010), BIOGRID (the Biological General Repository for Interaction Datasets) (Stark et al., 2011), and HPRD (Human Protein Reference Database) (Keshava Prasad et al., 2009).

Next, an ensemble PPI network was constructed by integrating 2 of the above-described PPI databases in mice. A total of 65,851 unique PPI pairs were collected, involving 10,951 unique proteins.

We extracted the gene expression profile data for the Dstn mutations with normal wild-type from Verdoni et al. (2008), which were deposited in NCBI (National Center for Biotechnology Information) GEO (Gene Expression Omnibus database, http://www.ncbi.nlm.nih.gov/geo/) database (ID: GSE9743). All mouse procedures were performed in accordance with the protocols approved by the Animal Care and Use Committee at the University of Wisconsin-Madison and conformed to the ARVO statement for the use of animals in Ophthalmic and Vision Research and APS's Guiding Principals in the Care and Use of Animals. The Dstn mutations and wild-type samples with 6 replications in each group were compared.

The Limma package in R language (Smyth, 2004) was used to identify DEGs. Background intensities were adjusted, and the original expression datasets from all conditions were processed into expression estimates using the RMA method with the default settings implemented in R (version 2.12.1) to construct the linear model. Only the DEGs with fold-change values greater than 1.5 and P values less than 0.05 were selected.

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Pathway crosstalk analysis

The crosstalk pathways are defined as those pathways that have overlapping genes and edges. The overlapping genes mean that both pathways are included, and the overlapping edges mean that both pathways included the PPI interaction edges.

To determine the co-expressed significance of a gene pair in disease cases, we used the Pearson correlation coefficient test to calculate the P value.

The P values were mapped to the nodes and edges of the PPI network collected from MINT. The following formula was used to define a function as the combination of the statistical significance of an interaction according to a scoring matrix. The detailed description can be found in Liu et al. (2010).

$$S(e) = f(diff(x), cor(x, y), diff(y))$$

$$= -2\sum_{i=1}^{k} \log_e(p_i)$$

Functions *diff*(*x*) and *diff*(*y*) are differential expression assessments of gene x and gene y, respectively. Function *cor*(*x*,*y*) represents the correlation between gene x and gene y. Method *f* is a general data integration method that can handle multiple data sources differing in statistical power. When k = 3, p1 and p2 are the P values of differential expression of 2 nodes, and p3 is the P value of their co-expression.

Significant pathways analysis

$$Sp = \sum_{e \in P} S(e)$$

The scores that are larger than Sp are used as the significance P value of pathway P to describe its importance.

We also used DAVID (Huang et al., 2009) for pathway-enrichment analysis for P values <0.05 as input into the DEG dataset.

Crosstalk analysis of relationships among pathways

The detailed crosstalk analysis of relationships among pathways was then investigated, especially that of overlap between 2 significant pathway analysis results.

To define the interaction significance between pathways, we summarize all the scores of edges S(e) of all non-empty overlaps. Specifically, the interaction score between 2 pathways was estimated by their overlapping status of weighted pathways using the following formula:

$$C(pi, pj) = \sum_{e \in \mathrm{Oij}} S(e),$$

where *Pi* and *Pj* are 2 pathways and *Oij* is their overlap.

To estimate the significance of the overlap between different pathways, we randomly sampled 10^5 times the same size of the 2 pathways from the edges of the pathway network and calculated their overlap scores. The frequency larger than C is regarded as the interaction significance P values. Finally, the crosstalk with P values <0.001 were considered to be significant.

Significant Gene Ontology (GO)-enrichment analysis of each pathway

The functional enrichment among proteins in 1 pathway is defined as follows:

$$P = 1 - \sum_{i=0}^{k-1} \frac{\binom{f}{i}\binom{n-f}{m-i}}{\binom{n}{m}},$$

where n is the number of nodes in the network, f is the number of proteins annotated with a particular GO function, m is the number of proteins involved in the pathway, and k is the frequency of the GO term. We identified the GO function enrichment of the pathways.

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RESULTS

In this study, the GSE9743 dataset was first downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/), and the R language was then used to calculate the DEGs. Based on the expression profiles, we utilized the PPI dataset and the KEGG pathways to elucidate significant pathways and the crosstalk among these significant pathways.

Significant pathway analysis

We used Sp to evaluate the importance of pathways (for details, see Material and Methods section). Thirty-six pathways (Table 1) were detected with P values <0.01.

Table 1. Significant pathway analysis.

ID	Node	Edge	Size	Score	P value	Description
mmu04623	3	49	64	869.37	0	Cytosolic DNA-sensing pathway
mmu05020	7	55	35	795.18	0	Prion diseases
mmu00052	10	115	29	1706.70	0	Galactose metabolism
mmu03450	11	150	13	1692.31	0	Non-homologous end-joining
mmu04114	11	31	114	739.21	0	Oocyte meiosis
mmu00100	12	60	18	1101.54	0	Steroid biosynthesis
mmu00500	15	131	48	1630.65	0	Starch and sucrose metabolism
mmu00630	19	187	19	2076.68	0	Glyoxylate and dicarboxylate metabolism
mmu04621	19	74	58	1190.49	0	NOD-like receptor signaling pathway
mmu04330	27	208	51	2758.92	0	Notch signaling pathway
mmu00970	34	473	65	6169.44	0	Aminoacyl-tRNA biosynthesis
mmu05220	34	273	74	3175.71	0	Chronic myeloid leukemia
mmu04622	47	1196	69	12312.19	0	RIG-I-like receptor signaling pathway
mmu03008	48	825	91	9438.96	0	Ribosome biogenesis in eukaryotes
mmu04662	55	831	77	8634.24	0	B cell receptor signaling pathway
mmu04810	65	318	218	3823.94	0	Regulation of actin cytoskeleton
mmu04722	79	1170	132	13045.08	0	Neurotrophin signaling pathway
mmu04110	97	883	128	11079.05	0	Cell cycle
mmu04010	128	521	269	5473.65	0	MAPK signaling pathway
mmu04510	151	1901	200	19541.14	0	Focal adhesion
mmu01100	360	1207	1202	12580.05	0	Metabolic pathways
mmu00900	8	73	15	899.86	1.00E-05	Terpenoid backbone biosynthesis
mmu04145	77	712	179	7202.11	1.00E-05	Phagosome
mmu04380	79	718	118	7221.60	6.00E-05	Osteoclast differentiation
mmu03430	21	336	22	3504.59	9.00E-05	Mismatch repair
mmu05200	107	422	326	4274.35	0.00049	Pathways in cancer
mmu04612	13	72	81	828.29	5.00E-04	Antigen processing and presentation
mmu05133	5	9	74	138.45	0.00057	Pertussis
mmu04070	2	11	78	160.22	0.00085	Phosphatidylinositol signaling system
mmu04666	7	23	92	297.94	0.00098	Fc gamma R-mediated phagocytosis
mmu05152	12	53	179	619.05	0.00113	Tuberculosis
mmu00562	34	181	57	1899.71	0.00136	Inositol phosphate metabolism
mmu04672	14	32	45	392.47	0.00154	Intestinal immune network for IgA production
mmu04130	26	154	35	1610.03	0.00359	SNARE interactions in vesicular transport
mmu04115	15	33	70	379.31	0.00851	p53 signaling pathway
mmu04916	7	13	101	164.38	0.00877	Melanogenesis

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The Limma package was used to detect 120 DEGs (for details, see Material and Methods section). Using DAVID with the DEGs, several pathways were identified. However, we only found 4 significant pathways: regulation of actin cytoskeleton (mmu04810) with a P value = 0.01, leukocyte transendothelial migration (mmu04670) with a P value = 0.001, tight junction (mmu04530) with a P value = 0.017, and arrhythmogenic right ventricular cardiomyopathy (mmu05412) with a P value = 0.04.

Remarkably, only 1 overlap of a significant pathway (regulation of actin cytoskeleton, mmu04810, marked red in Table 1), was detected in the Dstn mutations.

Crosstalk among the pathways

Further, we exploited the pathway crosstalk between regulation of actin cytoskeleton (mmu04810) and other significant pathways using the overlapping score. We found that 28 significant pathways cross-talked to the mmu04810 pathway (Table 2).

Table 2. Crosstalk between mmu04810 and corneal related pathways.

PathID_A	PathID_B	PathID_B_name	P value
mmu04810	mmu00052	Galactose metabolism	0
mmu04810	mmu00100	Steroid biosynthesis	0
mmu04810	mmu00500	Starch and sucrose metabolism	6.00E-05
mmu04810	mmu00970	Aminoacyl-tRNA biosynthesis	0
mmu04810	mmu01100	Metabolic pathways	0
mmu04810	mmu03008	Ribosome biogenesis in eukaryotes	0
mmu04810	mmu03450	Non-homologous end-joining	0.0018
mmu04810	mmu04070	Phosphatidylinositol signaling system	0
mmu04810	mmu04110	Cell cycle	0
mmu04810	mmu04114	Oocyte meiosis	0
mmu04810	mmu04115	p53 signaling pathway	0
mmu04810	mmu04145	Phagosome	0
mmu04810	mmu04330	Notch signaling pathway	0
mmu04810	mmu04380	Osteoclast differentiation	0.00026
mmu04810	mmu04510	Focal adhesion	0.00032
mmu04810	mmu04612	Antigen processing and presentation	1.00E-05
mmu04810	mmu04621	NOD-like receptor signaling pathway	0
mmu04810	mmu04622	RIG-I-like receptor signaling pathway	0
mmu04810	mmu04623	Cytosolic DNA-sensing pathway	0
mmu04810	mmu04666	Fc gamma R-mediated phagocytosis	0.00258
mmu04810	mmu04672	Intestinal immune network for IgA production	0.00426
mmu04810	mmu04722	Neurotrophin signaling pathway	2.00E-05
mmu04810	mmu04742	Taste transduction	0.00654
mmu04810	mmu04916	Melanogenesis	0
mmu04810	mmu05020	Prion diseases	2.00E-05
mmu04810	mmu05140	Leishmaniasis	0
mmu04810	mmu05152	Tuberculosis	0.00738
mmu04810	mmu05220	Chronic myeloid leukemia	0

Only high correlated pathways to the mmu04810 were listed in Table 2. The first two columns are the correlated pathways. The third column is the pathway name of the second column. The last column is the P value of two correlated pathways.

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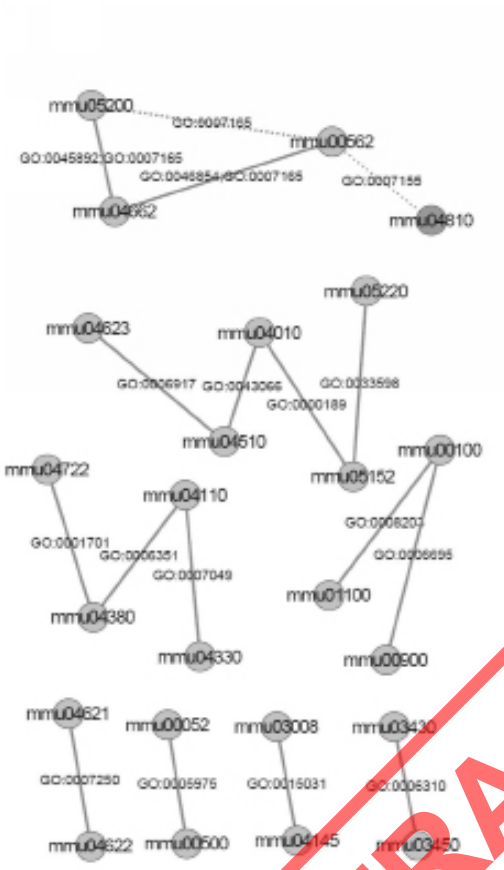
Crosstalk of GO relationships among pathways

For detailed analysis of the crosstalk between the significant pathways, we used the hypergeometric test to identify the significant GO terms of each pathway, with P values <0.05. The results of the top 5 GO terms in parts of the pathways were used to construct the connection among the pathways. In Figure 1, regulation of actin cytoskeleton (mmu04810) connected with inositol phosphate metabolism (mmu00562) through cell adhesion (GO: 007155), with a crosstalk P value <0.01.

Inositol phosphate metabolism (mmu00562), pathways in cancer (mmu05200), and B cell receptor signaling pathway (mmu04662) were connected through signal transduction (GO: 007165).

We also found that significant pathways, such as chronic myeloid leukemia (mmu05220), tuberculosis (mmu05152), MAPK signaling pathway (mmu04010), focal adhesion (mmu04510), and cytosolic DNA-sensing pathway (mu04623), were connected with mammary gland epithelial cell proliferation (GO: 0033598), MAPK import into nucleus (GO: 0000189), negative regulation of apoptosis (GO: 0043066), and induction of apoptosis (GO: 006917).

Based on the significant GO enrichments, we predicted the crosstalk between the GO biological processes during the disease development among the pathways.



ID	name
mmu00052	Galactose metabolism
mmu00100	Steroid biosynthesis
mmu00500	Starch and sucrose metabolism
mmu00562	Inositol phosphate metabolism
mmu00900	Terpenoid backbone biosynthesis
mmu01100	Metabolic pathways
mmu03008	Ribosome biogenesis in eukaryotes
mmu03430	Mismatch repair
mmu03450	Non-homologous end-joining
mmu04010	MAPK signaling pathway
mmu04110	Cell cycle
mmu04115	p53 signaling pathway
mmu04330	Notch signaling pathway
mmu04380	Osteoclast differentiation
mmu04510	Focal adhesion
mmu04621	NOD-like receptor signaling pathway
mmu04622	RIG-I-like receptor signaling pathway
mmu04623	Cytosolic DNA-sensing pathway
mmu04662	B cell receptor signaling pathway
mmu04722	Neurotrophin signaling pathway
mmu04810	Regulation of actin cytoskeleton
mmu05152	Tuberculosis
mmu05200	Pathways in cancer
mmu05220	Chronic myeloid leukemia

GOID	Description
GO:0006310	DNA recombination
GO:0007155	cell adhesion
GO:0007250	activation of NF-kappaB-inducing kinase activity
GO:0006351	transcription, DNA-dependent
GO:0007049	cell cycle
GO:0006695	cholesterol biosynthetic process
GO:0008203	cholesterol metabolic process
GO:0000189	MAPK import into nucleus
GO:0007165	signal transduction
GO:0006917	induction of apoptosis
GO:0033598	mammary gland epithelial cell proliferation
GO:0046854	phosphatidylinositol phosphorylation
GO:0015031	protein transport
GO:0005975	carbohydrate metabolic process
GO:0043066	negative regulation of apoptosis
GO:0001701	in utero embryonic development
GO:0045892	negative regulation of transcription, DNA-dependent

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Figure 1. Crosstalk with the overlap of top 5 GO terms of pathways. Significantly enriched GO biological processes are identified in every pathway. The edge of each pair of pathways represents the connection with the same GO terms. The solid lines mean the crosstalk's P value <0.01 and the dotted lines mean the P value >0.01.

DISCUSSION

Dstn^{corn1} mice exhibit an actin dynamic defect in corneal epithelial cells, offering an *in vivo* model to investigate cellular mechanisms affected by the Dstn mutation and resultant actin dynamic abnormalities. Microarray analysis using the cornea from Dstn^{corn1} and wild-type mice demonstrated that Dstn mutations have a strong influence on the gene expression profile, especially on the actin cytoskeleton regulator. As anticipated, regulation of the actin cytoskeleton (mmu04810) was also a significant pathway in our analysis. Furthermore, 28 significant pathways cross-talked to the mmu04810 pathway and were identified using the overlapping score (Table 2). Importantly, crosstalk analysis of GO relationships among pathways indicated that the mmu04810 pathway was indirectly connected to the mmu05200 pathway (pathways in cancer) and the mmu04662 pathway (B cell receptor signaling pathway) in a mmu00562

pathway-mediated manner (inositol phosphate metabolism). The results indicate that there are interaction relationships among these 4 pathways, which is in accordance with previous reports as follows.

Recent studies demonstrated that the organization and dynamics of the actin cytoskeleton could be regulated by the phosphoinositide pathway at several levels, such as phosphatidylinositol-3,4,5-trisphosphate (PIP3), phosphatidylinositol-4,5-bisphosphate (PIP2), and the enzymes catalyzing the production or hydrolysis of these lipids. Therefore, crosstalk between regulation of actin cytoskeleton and the phosphoinositide pathway is expected. Among the different PIs, PI(4,5)P2 is the best-characterized regulator of the actin cytoskeleton. PI(4,5)P2 interacts directly with several actin-binding proteins, such as ADF/cofilin, to regulate the activities of the actin-binding proteins (Zhao et al., 2010). Typically, PI(4,5)P2 inhibits actin-binding proteins that promote actin filament disassembly and activates proteins that induce actin filament assembly (van Rheenen et al., 2007). Therefore, PI(4,5)P2 is considered a promoter of the formation of actin filament structures beneath the plasma membrane and other phosphoinositide-rich membrane organelles. This is supported by a number of studies demonstrating that an increased plasma membrane PI(4,5)P2 level induces actin filament assembly in mammalian cells, while sequestration of PI(4,5)P2 leads to a defective cortical actin cytoskeleton (Saarikangas et al., 2010).

One study has demonstrated that there is a relationship between the regulation of the actin cytoskeleton and B cell receptor (BCR) signaling in the antigen processing and presentation process. Bruton's tyrosine kinase (Btk) is one linker connecting BCR signaling to actin dynamics. Using xid mice and a Btk inhibitor, BCR engagement increases actin polymerization and Wiskott-Aldrich syndrome protein (another actin-binding protein, similar to ADF/cofilin) activation in a Btk-dependent manner. Concurrently, Btk-dependent increases based on the level of PIP2, and phosphorylated Vav is observed upon BCR engagement. Thus, the BCR-triggered signaling regulates the dynamics of the actin cytoskeleton through WASP in a Btk-dependent manner (Sharma et al., 2009).

Cell hyperproliferation, inflammation, and angiogenesis are biological processes central to the pathogenesis of corneal disease, as well as other conditions including tumorigenesis and chronic inflammatory disorders. Therefore, pathways in cancer may be involved in the regulation of the actin cytoskeleton. In the past decade, many signaling pathways have been identified to be associated with cancer development, such as Ras/MAPK, MAPK/ERK, TGF-β, and PI3K (Dreesen and Brivanlou, 2007). These pathways have all been proposed to influence the regulation of the actin cytoskeleton. For example, the Ras/MAPK pathway is likely the critical pathway involved in cytoskeleton disruption during Ras transformation. Oncogenic Ras can specifically target the actin-based cytoskeleton and achieve morphological transformation of the cells by down-regulation of structural components of the cytoskeleton and inhibition of ROCKI/Rho kinase-dependent pathways (Pawlak and Helfman, 2002; Samaj et al., 2004). TGF-β, via Smad and p38Mapk, up-regulates expression of actin-binding proteins such as ADF/cofilin to regulate the actin cytoskeleton and cell motility in epithelial cells (Bakin et al., 2004; Vardouli et al., 2005; Moustakas and Heldin, 2008). One study demonstrated that the JNK and PI3K signaling cascades initiate in the early stages of angiogenesis through the reorganization of the actin cytoskeleton to increase production and activation of MMP-2. However, JNK mainly regulates the mRNA expression of MMP-2 and MT1-MMP, whereas PI3K regulates protein levels (Ispanovic and Haas, 2006).

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In conclusion, in this paper, a network-based approach was used to analyze the crosstalk between corneal related pathways. The crosstalk between the pathways was identified and analyzed using PPI datasets and expression profiles. The results are consistent with prior knowledge of actin dynamics. The crosstalk of pathways presents new alternative insights for corneal disease. As a comprehensive and system-wide analysis, our research may provide evidence for corneal disease and complements traditional component-based approaches.

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