A systematic review of genetic risk factors for neuropathic pain in adults with diabetes mellitus

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Introduction

- Neuropathic pain (NP) is a debilitating condition affecting 7-10% of the general population and 25% of people with diabetes mellitus (DM).
- There is large interindividual variation in the onset of NP in people with DM.
- Our previous systematic review identified genetic risk factors for NP, but no studies have attempted to collate the data specifically in people with DM.
- Identifying genetic risk factors will reveal the mechanisms that contribute to its development and help inform prevention and treatment.

Aims

- To conduct a systematic review to identify all published studies investigating genetic risk factors for chronic NP in adults with DM.
- To summarise the genetic risk factors for chronic NP in DM through narrative synthesis.

Methods

Design

- PROSPERO ID: CRD42022335554

Databases

- Cochrane, Embase (Ovid), PubMed, Scopus and Web of Science

Screening

- Title/abstract and full-text screening was conducted by two reviewers.

Risk of bias

- Studies assessed by two reviewers using Q-GENIE.

Table 1 – Study criteria using the PICO framework

Parameter	Inclusions	Exclusions
Population	- Participants ≥ 18 years - Diabetes (any type)	- Participants < 18 years - Animal studies - Non-diabetics
Exposure	- Genetic factors (risk variant)	n/a
Control	- Genetic factors (reference variant)	n/a
Outcomes	- Neuropathic pain (presence/absence) - Duration ≥ 3 months	n/a
Time Scale	- Up to 17th June 2023	n/a
Study Type	- Candidate gene association study - Genome-wide association study - Targeted/whole genome Sequencing	- Case study or series - Conference abstracts - Studies without access to full-text - Studies not in English

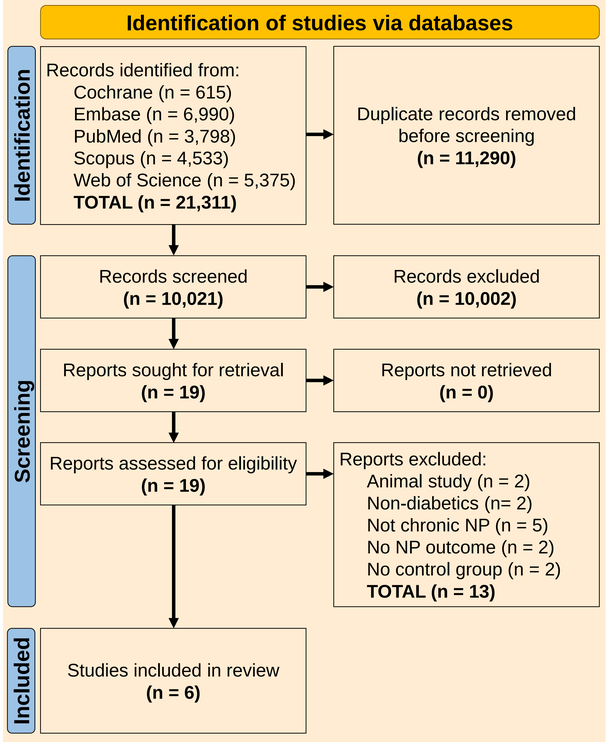

Figure 1 – PRISMA flow chart

Results

Table 2 – Study characteristics

Study	Type	NP Outcome	Sample size (cases/controls)	Quality Rating*
Almomani R *et al*. 2023	Targeted sequencing	pDN	237/309	Moderate
Alsaloum M *et al*. 2019	Targeted sequencing	pDN	230/317	Moderate
Blesneac I *et al*. 2018	Targeted sequencing	pDN	111/78	Moderate
Sleczkowska M *et al*. 2022	Targeted sequencing	pDN	222/304	Moderate
Veluchamy A *et al*. 2021	GWAS	General NP	383/420	Good
Wadhawan S *et al*. 2017	Targeted sequencing	pDN	138/41	Moderate

GWAS, genome-wide association study; NP, neuropathic pain; pDN, painful diabetic neuropathy
*Based on Q-GENIE

Table 3 – Rare potentially pathogenic variants identified in people with DM with and without neuropathic pain

Transporter Pathway	Gene	Chromosome	Number of variants (NP/no NP)	Number of studies
Sodium Channel	*SCN3A*	2	3/3	1
	SCN7A	2	6/3	1
	SCN8A	12	2/2	1
	SCN9A	2	21/9	3
	SCN10A	3	11/17	2
	SCN11A	3	4/5	1
	SCN1B	19	1/1	1
	SCN2B	11	2/2	2
	SCN3B	11	1/1	1
Chloride channel	*ANO1*	11	0/1	1
	ANO3	11	3/0	1
Potassium channel	*KCNK18*	10	2/2	1
	KCNQ3	8	0/1	1
	HCN1	5	1/0	1
Cation channel	*TRPA1*	8	3/2	1
	TRPM8	2	3/1	1
	TRPV1	17	0/3	1
	TRPV4	12	1/3	1

DM, diabetes mellitus; NP, neuropathic pain

Discussion

Conclusions

- The findings demonstrate a potential role of genetic factors in the onset of NP in people with DM.
- However, further high-powered studies are needed with consistent case definition and statistical analysis, particularly genome-wide association studies.
- Non-genetic factors are also being investigated in a separate systematic review.

Relevance for Patient Care

- Elucidating the genetics underpinning NP in DM may lead to the development of new therapies and enable patient stratification that will inform both prevention and treatment.

References

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