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REVOLUTIONISING MEDICINE - THE NEW FRONTIER

Effects of MODY and Asian-specific Type 2 diabetes susceptibility gene (PAX4) interaction on the clinical manifestations of young-onset diabetes

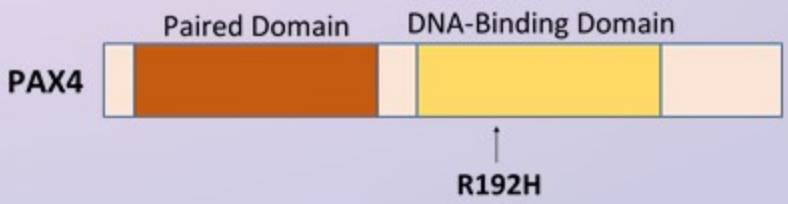
Ang SF[1], Tan SHC[1], Goh LX[1], Chan LWT[1], Kon WYC[2], Rashida Farhad[3], Loh WJ[4], Lim SC[1]

1 Khoo Teck Puat Hospital, National Healthcare Group
2 Tan Tock Seng Hospital
3 KK Women's and Children's Hospital, SingHealth
4 Changi General Hospital, SingHealth

Background & Aims

- Diabetes is an evolving global epidemic. Monogenic and complex forms of diabetes are thought to be etiologically disparate although they share overlapping clinical features.
- Among our young-onset Type 2 diabetes (YT2D) patients identified for monogenic diabetes/MODY genetic testing, we observed that PAX4 R192H, a strong Asian-specific T2D susceptibility variant (reported OR ~1.79), was present in ~25% of the patients.
- A proportion of these patients also carried a deleterious variant of MODY as annotated based on ACMG guidelines.
- Therefore, we hypothesize that such gene-gene interaction results in clinical heterogeneity and aim to determine the phenotypic effect of this interaction in our cohort.

Introduction



- PAX4 (Paired box 4) is a transcription factor expressed early during development and is important for β-cell differentiation[1-2].
- R192H was shown to repress insulin and glucagon expression in in-vitro experiments[3].
- R192H associated with T2D[4-6] (Odds ratio of 1.79)[4] and younger onset of diabetes in Chinese[5].
- Allele frequency in dbSNP and ExAC (East Asians) is 7% and 10%.
- 2 out of 4 in silico analysis tools (SIFT & Polyphen2) predicted the variant to be deleterious.
- Conserved amino acid substitution in the DNA binding domain.
- **T2D risk factor in East Asians** [4-5] and **younger onset of T2D** in Singapore East Asians[7].

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Methodology

- As part of our monogenic diabetes research study, patients were recruited based on their clinical phenotypes for targeted re-sequencing/genotyping of 17 candidate MODY genes using next-generation sequencing/TaqMan genotyping assay.
- Genetic variants were classified according to American College of Genetics and Genomic (ACMG) guidelines. Statistical analysis was performed using SPSS Ver. 27.

Results

Clinical characteristic % or Median (IQR)	PAX4 R192H+ MODY (n=9)	PAX4 R192H only (n=40)	MODY only (n=29)
Male gender	33.3%	55.0%	31.0%
Ethnicity			
Chinese	100.0%	90.5%	69.0%
Malay	0%	2.5%	10.3%
Indian	0%	0%	17.2%
Others	0%	7.5%	3.4%
Age (years)	30.4 (21.0-35.5)	39.5 (30.0-50.8)	36.8 (24.5-46.5)
Age of onset (years)	20.4 (16.5-25.0)	27.3 (19.5-35.0)	21.0 (17.3-27.0)
Diabetes duration (years)	7.0 (2.0-17.5)	11.0 (3.3-18.8)	10.0 (3.0-25.0)
BMI (kg/m²)	20.4 (18.8-23.7)	25.1 (21.6-26.9)	22.4 (20.0-25.0)
Waist circumference (cm)	74.0 (64.0-75.5)	84.0 (70.8-92.0)	76.0 (66.0-82.0)
HbA1c (%)	6.8 (6.4-9.7)	7.9 (7.7-9.0)	7.8 (6.7-9.7)
Insulin (% Yes)	11.1%	55.0%	62.1%
SBP (mmHg)	123 (107-130)	123 (113-135)	126 (114-143)
DBP (mmHg)	70 (65-79)	76 (71-85)	78 (69-84)
Total cholesterol (mM)	4.72 (3.67-5.16)	4.32 (3.85-4.84)	4.54 (3.64-5.27)
HDL (mM)	1.67 (1.20-2.11)	1.28 (1.06-1.46)	1.49 (1.10-1.74)
LDL (mM)	2.70 (1.84-3.23)	2.70 (2.18-3.28)	2.62 (2.20-3.37)
Triglycerides (mM)	0.75 (0.68-1.69)	1.37 (0.83-1.81)	0.98 (0.78-1.50)

Patients with *PAX4* R192H only (n=40) have higher BMI (+2.63 kg/m², 95% CI [0.43, 4.84], p=0.019), higher waist circumference (+7.97 cm, 95% CI [0.16, 15.77], p=0.045), older age of onset (+6.31 years, 95% CI [0.17, 12.46], p=0.044), and more likely to be on insulin treatment (OR: 9.49, 95% CI [1.05, 85.78], p=0.045) than patients with simultaneous *PAX4* R192H and MODY deleterious variants (n=9) after adjusting for gender and ethnicity.

They also have higher BMI (+2.20 kg/m², 95% CI [0.46, 3.94], p=0.013), higher waist circumference (+5.83 cm, 95% CI [0.003, 11.65], p=0.049) and older age of onset (+5.81 years, 95% CI [1.30, 10.33], p=0.012) than patients with MODY deleterious variants only (n=29).

Conclusions

- Overall, patients with only *PAX4* R192H have worse metabolic profiles resembling more of T2D than patients with MODY deleterious variants (with/without *PAX4* R192H).
- Disease manifestation is affected by an interplay of multiple genetic factors and they should be evaluated together in diabetes stratification and management.

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