Pharmacogenetic (PG) Investigation of Hypersensitivity to Abacavir

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Abstract

Abacavir (ABC) is an effective antiretroviral drug. In the totality of ABC clinical studies, the overall rate of suspected ABC hypersensitivity reaction (HSR) was 5.4%.[1] In rare cases, HSR has proved fatal. A clinical risk management program has successfully reduced the rate of serious outcomes. Pharmacogenetic (PG) research, involving over 500 clinically suspected ABC HSR cases and over 700 ABC tolerant controls has been completed. In Caucasian subjects, the HLA-B*5701 allele was confirmed as the most predictive individual genetic marker and no marker pairs or combinations had superior performance characteristics. In non-Caucasians, the sensitivity of HLA-B*5701 as a predictor of clinically suspected HSR ranged from 8% in Blacks to 57% in Thai Asians. GSK has initiated two clinical studies in which skin patch testing will be used to augment the clinical diagnosis of ABC HSR. PREDICT-1 will evaluate the impact of HLA-B*5701 screening on the incidence of ABC HSR. SHAPE will estimate the sensitivity of HLA-B*5701 in Caucasian Americans and in African Americans. Clinical management must remain the basis for the diagnosis and management of ABC HSR. Over-reliance on prognostic markers could lead to reduced clinical vigilance and more serious outcomes.

Introduction

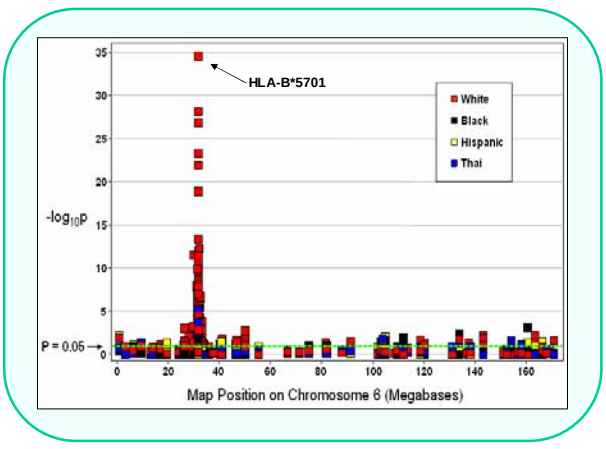
- **Abacavir (ABC) is an effective antiretroviral drug.**
- **In clinical studies to date, 5.4% of patients have experienced a suspected HSR[1].**
- **A clinical risk management program has successfully reduced the incidence of serious outcomes.**
- **A highly predictive genetic marker could improve the benefit to risk ratio of ABC.**
- **HLA-B*5701, has been shown to be highly associated with ABC HSR in multiple studies of Caucasian patients.[2, 3, 4]**
- **Estimates of the sensitivity of HLA-B*5701 in Caucasians vary from study to study: 48%[2] to 94%[4].**
- **Research Questions:**
  - **Are there genetic markers other than HLA-B*5701 that are predictive of ABC HSR?**
  - **Are there other genetic markers that, when considered in combination with HLA-B*5701, can enhance its predictive values?**
  - **How predictive is HLA-B*5701 in non-Caucasian patient groups?**

Methods

- **Subjects**
  - **From 5 clinical studies**
  - **595 "Cases" – Retrospectively identified subjects with clinically suspected ABC HSR**
  - **744 "Controls" – ABC treated subjects with no evidence of ABC HSR**
  - **Self-reported racial affiliation: Caucasian (73%), Black (9%), Hispanic (10%), and Asian (8%, from Study EPV40001, conducted in Thailand)**
  - **Average Age: 40.9, Gender: 24% were Female**
- **Genetic Markers**
  - **Candidate genes: Drug metabolism, immune response**
  - **Genome-wide genetic markers: >1.5 million**
- **Statistical Methods**
  - **Hardy-Weinberg Equilibrium testing**
  - **Genotypic association with HSR (Fisher's Exact Test)**
  - **Per-marker performance characteristics: sensitivity and specificity**
  - **Per-marker positive and negative predictive values**
  - **Marker pair performance characteristics**
  - **Racial groups analyzed separately**

Results

Figure 1. Association P-values By Chromosome 6 Location



- **Significant associations with suspected ABC HSR were found for markers located throughout the genome.**
- **The strongest associations were for markers located on chromosome 6 in the region surrounding HLA-B.**

Acknowledgements

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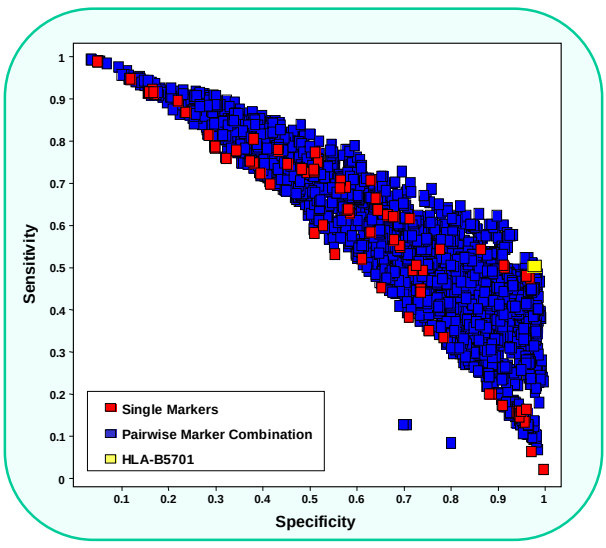
Results (continued)

Figure 2. Sensitivity vs Specificity of Replicated Markers and Pairwise Marker Combinations (Caucasian Subjects)



- **84 genetic markers (Figure 2, red squares) demonstrated association with clinically suspected ABC HSR in two separate sets of Caucasian study participants.**
- **In Caucasian participants, HLA-B*5701 was the marker most highly associated with clinically suspected ABC HSR (sensitivity=50%, specificity=98%, p=10^{-73}).**
- **In Caucasian participants, no combination of markers exhibited a sensitivity and a specificity greater than those of HLA-B*5701 alone.**

Table 1. Performance Characteristics of HLA-B*5701, By Racial Group

Racial Group	Cases	Controls	Genotypic P-value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio	Odds Ratio 95% CI
Caucasian	444	486	7.5×10^{-73}	50%	98%	53%	97%	42.1	(22.8, 77.8)
Black	50	67	0.16	8%	99%	14%	96%	4.3	(0.7, 28.3)
Hispanic	63	70	1.2×10^{-5}	22%	95%	67%	95%	41.3	(2.4, 708.7)
Asian (Thai)	7	102	6.3×10^{-6}	57%	99%	87%	99%	263.6	(11.0, 5909.1)

- **In non-Caucasians, sensitivity of HLA-B*5701 varied from 57% in Thai (n=7 cases), to 22% in Hispanic (n=63 cases), to 8% in Black subjects (n=50 cases).**

Discussion

- **Retrospective assessment of ABC HSR is difficult**
- **Skin patch testing, a research tool not clinically validated, might improve diagnostic accuracy of ABC HSR.**
- **Two GSK studies that incorporate skin patch testing have commenced.**
  - **The PREDICT-1 Study: A prospective study that will compare the ABC HSR rate between a standard-of-care ABC treatment group and a cohort of patients who do not carry the HLA-B*5701 allele.**
  - **The SHAPE Study: A retrospective case-control study to evaluate the performance characteristics of HLA-B*5701 in Caucasian and African Americans.**
- **Symptoms of HSR may overlap with other syndromes; thus, diagnosis can be complicated by concurrent diseases or adverse events from concomitant drugs.**
- **Clinical management must remain the basis for diagnosis and management of ABC HSR.**
- **Over-reliance on prognostic markers could lead to reduced clinical vigilance and more serious outcomes.**

Conclusions

- **A strong association between clinically suspected ABC HSR and HLA-B*5701 carriage in Caucasians was confirmed.**
- **No other single marker and no marker pair featured a sensitivity and specificity greater than those for HLA-B*5701.**
- **Results in non-Caucasians are considered exploratory due to reduced sample sizes**
  - **HLA-B*5701 was the marker mostly highly associated with clinically suspected HSR in Hispanics and Thai Asians.**
  - **Evidence for association of HLA-B*5701 and clinically suspected HSR among Black subjects was limited.**
- **Further research is warranted to investigate variation in performance characteristics of HLA-B*5701 observed among different Caucasian study sets and among patient groups of different racial affiliation.**

References

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