

# 278 - Metabolism

## Metabolism

276 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 HLA-B59:01 Presence of allele highly predictive of agranulocytosis but is rare in East Asian populations and almost absent in people of European descent. Sensitivity 31.8%, specificity 95.3%.<sup>6</sup> PPV 6.4%, NPV 99.3%. HLA DQB1/HLA-B Single amino acid changes HLA DQB1 126Q and HLA-B 158T associated with increased risk of agranulocytosis. Overall, 39 of 95 cases had one or both alleles; 175 of 206 controls had neither allele. Sensitivity 41.0%, specificity 85.0%<sup>7,8</sup> (36% and 89% figures given elsewhere).<sup>9</sup> PPV/NPV not given but can be calculated. HLA-DRB1 DRB104:02 confers a six-fold higher risk of agranulocytosis. NPV is 99.3%.<sup>10</sup> The HLA-DQB1 variants and the HLA-B variants are in linkage disequilibrium<sup>9</sup> and are likely to convey the same association signal. Variants in linkage disequilibrium are inherited together. Benign ethnic neutropenia ACKR1 rs2814778 CC genotype at rs2814778 (Duffy Null Status) is considered to be the cause of BEN.<sup>11</sup> All patients starting clozapine should undergo genetic testing for BEN.<sup>12</sup> Metabolism Clozapine is largely metabolised by CYP1A2 and, to a lesser extent in most people, CYP3A4/5. Despite early reports, CYP2D6 plays almost no role in the metabolism of clozapine.<sup>13</sup> Metabolic rate is usually classified as poor (PM), intermediate (IM) or extensive (EM) and each is associated with a particular genetic variant. Genetic analysis can therefore allow an estimate of the target dose of clozapine for an individual. This is the most accurate method of predicting clozapine dose.<sup>14</sup> Cytochrome p4501A2 PM/IM/EM status as normally defined by analysis of e.g. CYP1A2\*1F/1C/1A/1K.<sup>15</sup> Cytochrome p4503A4 PM/IM/EM status. CYP3A4 is usually a minor route of clozapine metabolism but metaboliser status affects blood concentration.<sup>16</sup> Cytochrome p4503A5 PM/IM/EM status. CYP3A5 PM status associated with elevated clozapine blood levels.<sup>17</sup> Other non-CYP genetic associations have also been demonstrated.

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